The lung function, hemoglobin concentration and arterial oxygen saturation among 9-10 year old native Tibetan and Han Chinese children living at 3700meters and 4300meters above sea level in Tibet

GONGGALANZI

Supervisor:
Professor Espen Bjertness, PhD
Head, Section for Preventive Medicine and Epidemiology

Co-supervisor:
Sveinung Berntsen, PhD student
Norwegian School of Sport Sciences

University of Oslo
Faculty of Medicine
Department of General Practice and Community Medicine

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TERMINOLOGY AND ABBREVIATIONS

Adaptation – a characteristic of an organism that has been favored by natural selection and increases the fitness of its possessor. Any change in the structure or functioning of an organism that makes it live and reproduce to a given environment (1).

Altitude acclimatization – the process of adjusting to decreasing oxygen levels at higher elevations, in order to avoid altitude sickness (1).

Arterial oxygen saturation (SaO_2) - the percent of the heme (the deep red, non-protein, ferrous component of hemoglobin) groups in the hemoglobin molecule in the blood which are bound with oxygen (1).

Cardiac output - the volume of blood pumped by the heart per minute. It is the product of heart rate (beats/minute) and stroke volume (milliliters/beat). Stroke volume, in turn, is regulated by pre-load (right and left heart filling pressures), myocardial contractility (the percent of the ventricular volume expelled/beat), and after load (pulmonary and systemic blood pressure or vascular resistance) (1).

Cor pulmonale - Failure of the right side of the heart caused by prolonged high blood pressure in the pulmonary artery (called pulmonary hypertension) and right ventricle of the heart (2).

Forced expiratory volume in 1 seconds (FEV_1) - This measures the amount of air you can exhale with force in one breath. The amount of air you exhale measured at 1 second (FEV_1), usually expressed in *liter* (3).

Forced vital capacity (FVC) - This measures the amount of air you can exhale with force after you inhale as deeply as possible, usually expressed in *liter* (3).

Forced expiratory flow 50% (FEF_{50}) - This measures the air flow halfway through an exhale (FVC), usually expressed in *liter/second* (3).

Hemoglobin concentration ([Hb]) - the concentration of hemoglobin in the blood, usually expressed in *g/dl*. It is comprised of hemoglobin able to bind or release oxygen (oxyhemoglobin, deoxyhemoglobin) as well as hemoglobin bound to other substances or unable to bind oxygen (carboxyhemoglobin, methemoglobin) (1).

Hemoglobin-oxygen affinity - the extent to which oxygen is tightly bound to hemoglobin. This varies depending on the amount of oxygen present and the temperature, the pH, and the presence of other compounds in the blood. It is measured as the position of the hemoglobin-oxygen dissociation curve, often indexed as the P50 or the oxygen pressure at which hemoglobin is half-saturated with oxygen (1).

Hypoxia - means "a deficiency in oxygen." It can refer to a shortage of oxygen in the body due to low barometric pressure (4).

Hypoxemia – Reduced oxygen delivery to the tissues as the result of lower blood oxygen content or reduced tissue blood flow (1).

Polycythemia - a condition in which there are too many red blood cells in the blood circulation. It is the opposite of anemia, which results from too few red blood cells in the blood circulation. It is also called erythrocytosis (5).

Pulmonary hypertension - a rare lung disorder characterized by increased pressure in the pulmonary artery. The pulmonary artery carries oxygen-poor blood from the lower chamber on the right side of the heart (right ventricle) to the lungs where it picks up oxygen (6).

Ventilation - the amount of air expired out per minute. It is also called minute or resting ventilation and is expressed in liters BTPS (body temperature pressure saturated) /minute. It includes air moving through the alveoli (areas of gas exchange) and dead space (bronchi, trachea), referred to as alveolar ventilation and dead space ventilation (1).

L- liter

m – meter

BMI - Body mass index

TAR – Tibet Autonomous Region

ABSTRACT

***Aim*:** Chronic mountain sickness (CMS) is more common among Han Chinese immigrants who have immigrated from inland China (from low altitude to high altitude Tibet) than among native Tibetans living at the same altitude. The prevalence of CMS is higher in inhabitants who live at a higher altitude compared to those who live at lower altitude in Tibet. However, there is still no definite answer to the question why CMS occurs. Early detection of risk factors in CMS is solicitously needed. Therefore, the aim of the present study is to give descriptive data and to investigate possible differences between native Tibetan and Han Chinese children living in Lhasa at 3700 meters above sea level and native Tibetan children living in Tingri at 4300 meters above sea level, with respect to selected factors, which may increase the risk of development of CMS, such as lung function, hemoglobin concentration, and arterial oxygen saturation.

Methods: Two cross sectional studies were conducted among 9-10 year old Tibetan (n=406) and Chinese (n=406) children living at 3700 meters (Lhasa) in 2005, and the same age for Tibetan children (n=444) living at 4300 meters (Tingri) in 2007. A total of 1256 (667 boys and 589 girls) children participated. Lung function including Forced expiratory volume in 1 seconds (FEV1), Forced vital capacity (FVC) and Forced expiratory flow 50% (FEF_{50}), hemoglobin concentration, and arterial oxygen saturation at rest were measured using standard methods. Heart rate and anthropometric measurements were also recorded. Questions about demographic characteristic, parental smoking, diet, socioeconomic factors and physical activity were provided from a questionnaire.

***Results*:** After adjusting lung function values for sex, age, weight, height and duration of living in Tibet, Tingri Tibetan children had statistically significant higher FEV_1 and FVC values than Lhasa Tibetan children who had significantly higher values than Lhasa Chinese children (Tingri Tibetan vs. Lhasa Tibetan vs. Lhasa Chinese: FEV_1: 1.86 (1.83-1.88)L vs.1.76 (1.74-1.78)L vs.1.66 (1.63-1.68) L; FVC: 2.13 (2.10-2.16)L vs.1.97 (1.94-1.99)L vs.1.88 (1.85-1.91) L). Both native Tingri Tibetan and Lhasa Tibetan children had significantly higher FEF_{50} than Han Chinese children (Tingri Tibetan vs. Lhasa Tibetan vs. Lhasa Chinese: 2.76 (2.67-2.85)L/s vs.

2.72 (2.64-2.79)L/s vs. 2.35 (2.27-2.44) L/s). The difference was not statistically significant between Tingri and Lhasa Tibetan children for FEF_{50}.

Tingri Tibetan children had statistically significant lower hemoglobin concentration compared to Lhasa Tibetan children who had significantly lower hemoglobin concentration than Lhasa Han Chinese children (Tingri Tibetan vs. Lhasa Tibetan vs. Lhasa Chinese: 14.0 (13.9-14.1) g/dl vs.14.6 (14.5-14.7) g/dl vs.15.3 (15.2-15.5) g/dl).

There were no differences between Tingri Tibetan, Lhasa Tibetan and Lhasa Chinese in heart rate at rest. Tingri Tibetan children had significantly lower arterial oxygen saturation than both Lhasa Tibetan (Tingri Tibetan vs. Lhasa Tibetan: 87.2 (86.7-87.8) % vs. 91.1 (90.8-91.3) %, $p<0.001$) and Lhasa Han Chinese children (Tingri Tibetan vs. Lhasa Han Chinese: 87.2 (86.7-87.8) % vs. 90.4 (90.1-90.7) %, $p<0.001$). Lhasa Tibetan girls had higher arterial oxygen saturation than Lhasa Han Chinese girls (girls: 91.1 (90.7-91.5) % vs. 90.2 (89.6-90.7) %, $p<0.05$). But for boys there was no difference.

Conclusion: Tingri Tibetan children (4300m) had better lung function values FEV_1, FVC and FEF_{50} and lower crude haemoglobin concentration than Lhasa children (3700m). The FEF_{50} difference between Tingri Tibetan and Lhasa Tibetan children was, however, not statistically significant. If poor lung function is associated with increased risk of CMS at old age, the results may indicate that Tingri Tibetan children have lower risk of CMS than Lhasa children. At the same altitude (3700 m), Lhasa Chinese children had lower lung function values FEV_1, FVC and $FEF_{50,}$ and higher crude haemoglobin concentration than Lhasa Tibetan, also seems that Lhasa Han Chinese will have a higher risk of later development CMS. A prospective study, following the children to the age when CMS occurs would give answers to this hypothesis. However, it is more likely that other factors modify the risk during the years up to adulthood, resulting in higher risk of CMS with increasing altitude. Regarding haemoglobin concentration and arterial oxygen saturation, more analyses on adjusted values need to be done in order to conclude the possible differences between groups.

CHAPTER I

BACKGROUND AND INTRODUCTION

I BACKGROUND AND INTRODUCTION

1 Background

The highland areas of the world are populated by a considerable number of people. More than 140 million people worldwide live higher than 2500 m above sea level (7). With increasing altitude, less oxygen enters the lung when breathing , and thus, causes an inadequate supply of oxygen to the body which may lead to hypoxia (8). Highlanders are adapted to a hypobaric hypoxia environment, but those who lose the adaptation capability may develop Chronic Mountain Sickness (CMS) (9). CMS affects the quality of life, mental and physical performance and very likely leads to premature death and accounts for a substantial morbidity burden among high altitude populations (10). Therefore, CMS has been considered a public health concern in high altitude regions around the world.

In a sub sample of people living at high altitude, the appropriate erythrocytotic response may becomes excessive (i.e. excessive erythrocytosis) (11). Excessive erythrocytosis response is a risk factor for CMS and also included in the diagnostic criteria for CMS (9). From the studies which have been conducted in the mountainous regions around the world, the prevalence of excessive erythrocytosis in Cerro de Pasco of Peru at 4340 m increased from 6.8% in the youngest group (20 to 29 years of age) to 33.7% in the oldest group (60 to 69 years of age) with an average prevalence of 15.6% (12). Bolivian investigators reported a CMS prevalence of 6% to 8% in the male population of La Paz (3600 m) (13). Studies in Kyrgyzstan found electrocardiogram signs of cor pulmonale (a change in the structure and function of the right ventricle of the heart, which may be due to a chronic hypoxic pulmonary vasoconstriction) are 14% among subjects aged 16 to 75 years living in the Naryn area (2800 to 3100 m) (14).

In Tibet, most of the population lives at altitudes higher than 3,500 meters above sea level. The overall prevalence of CMS in the population older than 15 years is estimated to be 1.2% in native Tibetans and 5.6% in immigrated Chinese from inland China (15). Furthermore, the prevalence of CMS increases progressively as altitude increases. The prevalence is 0 % at 2260 to 2800m in both male and female Tibetans; 0.8 % at 3050 to 3800 m and 3.0 % at 4000 to 5200 m in Tibetan male, 0.3 % at 3050 to 3800 m and 1.6 % at 4000 to 5200 m in Tibetan female (1). It is likely that the difference in CMS prevalence at different altitudes is due to differences in some factors related to the ability of keeping adapted and/or to acclimatize to high altitude.

A broader understanding of potential risk factors of CMS is of importance for the millions of people who live at high altitude and are at risk for developing CMS. Studies on populations living permanently in high-altitude environments have shown some peculiarities of the respiratory, cardiovascular, and hematological systems (16). Several scientists have done studies on how Tibetan people have adapted to such a high elevation, but there is still no definite answer to the question why CMS occurs. Most of the researches related to CMS have been done in small samples, and often very wide age groups are included. Data are scarce for children and adolescents. We know that in high-altitude dwellers excessive erythrocytotic is involved in the mechanism of development of CMS. For some lifestyle diseases, like cardiovascular diseases, profiles of risk factors have already been detected at the age of 9 year old children (17). It is not known if such profiles for CMS-risk factors exist in Tibetan children. The ideal design of studying risk factors of CMS would have been to follow a large sample of adolescents living at high altitude, with regular measurements for many years and to compare those who develop CMS and those who do not. However, as far as we are aware there are no studies on 9-10 year old children living at different level of high altitude of sufficient sample size which include both measurements of lung function, hemoglobin concentration and arterial oxygen saturation.

The present thesis focuses on the research question: what are the differences between children living at 3700 meters above sea level (Lhasa) and 4300 meters above sea level (Tingri) with respect to selected factors, which may be associated with the ability to adapt and/or keep adapted, and more broader to live at high altitude, such as lung function, hemoglobin concentration and arterial oxygen saturation. Data on hemoglobin concentration, arterial oxygen saturation from Lhasa has previously been published in an M.Phil thesis (18), while the lung function data has not. Similar data from Tingri has been collected as a part of the present thesis, and will be used for a comparison with data from Lhasa. The present thesis is a part of a comprehensive study on chronic mountain sickness in Tibetthat started in 2004.

The present study will provide data which may contribute to the understanding of CMS and be utilized for the purpose of increasing the awareness of CMS and its public health consequences.

2 Introduction

2.1 High altitude regions

High altitude is in the range of: 8,000 - 12,000 feet (2,438 - 3,658 meters); very high altitude: 12,000 - 18,000 feet (3,658 - 5,487 meters); and extremely high altitude: 18,000+ feet (5,500+ meters) (19). The three main high-altitude regions in the world are the Himalayas of Asia, the Andes of South America and the Rocky Mountains of North America.

The Himalayan (Qinghai–Tibetan) Plateau is the highest and largest plateau in the world, it was uplifted by the collision between the Eurasian continent and India Sub-continent. Having a mean elevation of over 4,000 meters and an area of about 2,072,000 km^2 (20) (for more details see appendix I). The Andean altiplano lies in the central regions of the Andes Mountains and extends from central Peru into Bolivia. This plateau which ranges between 3000 and 4500m encompasses nearly 1,036,000 km^2 (21). The Rocky Mountains begin in northern Mexico, where the axial crystalline rocks rise to 3,700 m between the horizontal structures of the plains on the east and the plateaus on the west and encompassing nearly 388,500 km^2 (22). Among these three regions, Tibetans have lived the longest time, about 50,000 years at the Qinghai–Tibetan Plateau , followed by Andeans who have lived in the Andean altiplano about 9,000-12,000 years, then Europeans who inhabited permanently from about 150 years in the Rocky Mountain region (1). In Tibet, there has been an influx of Han Chinese immigrants from inland China since during the last 100 years. As of 2005, more than 179 thousand Chinese live permanently in Tibet. After the opening of the railway between Golmud and Lhasa in 2006, the immigration has increased considerably (23).

2.2 Definition of chronic mountain sickness

Chronic mountain sickness was first described by Dr. Monge in 1928 (24), and is often referred to as "Monge's disease". **CMS or Monge's disease** has been defined by a recent international consensus as a clinical syndrome that occurs to native or long-life residents above 2500 m. It is characterized by excessive erythrocytosis (females, Hb ≥ 19 g/dL ; males, Hb ≥ 21 g/dL), severe hypoxemia, and in some cases moderate or severe pulmonary hypertension, which may evolve to cor pulmonale, leading to congestive heart failure. The clinical picture of CMS gradually disappears after descending to low altitude and reappears after returning to high altitude (7).

The Chinese criteria of CMS which has been widely used in order to assess CMS severity and to compare CMS cases within and between different countries in the world is shown in table 1 (15).

Table 1. The Chinese criteria for chronic mountain symptoms and signs (15).

symptom \ score \ frequency	**negative**	**mild appearance**	**moderate appearance**	**severe appearance**
Headache	0	1	2	3
Dizziness	0	1	2	3
Failing memory	0	1	2	3
Fatigue	0	1	2	3
breathlessness/or palpitations sleep disturbances	0	1	2	3
Tinnitus	0	1	2	3
Anorexia	0	1	2	3
cyanosis of lips	0	1	2	3
face or fingers	0	1	2	3
hyperemia and prominent capillaries of conjunctivae or laryngopharynx	0	1	2	3

In addition to the 10 symptoms and signs, the following level of hemoglobin concentration and arterial oxygen saturation are included in the in the diagnosis:

Hemoglobin concentration in male: 18 g/dL <Hb <21 g/dL: score=0; Hb≥21 g/dL: score=3. In female: 16 g/dL <Hb <19 g/dL: score=0, Hb≥19 g/dL: score=3. Arterial oxygen saturation (SaO_2): ≤85%: score=3 in both gender.

Based on the grading of the ten symptoms and signs, hemoglobin concentration (Hb) and arterial oxygen saturation (SaO_2), CMS is defined as absent (Score 0-5); mild (score 6-10); moderate (score 11-14); and severe (score ≥15). Patients with severe headache, (Hb) ≥ 25.0 g/dl, and SaO_2 ≤ 85% with an overall score ≥ 15, indicate severe CMS and should immediately move down to lower altitude (15).

2.3 Mechanisms of developing CMS

As a consequence of hypobaric hypoxic environment, human residents at high altitudes will start the normal compensatory mechanism of hyperventilation due to a lowered partial inspiratory oxygen tension, which is an attempt to increase the arterial oxygen partial pressure (PaO_2 in mmHg) (25). However, a gradual reduction of hyperventilation is the probable initial mechanism of a cascade of events that leads to progressive deterioration of adaptation and to the development of CMS. A low level of alveolar ventilation leads to hypoxemia which means lack of oxygen in the blood (7). Low supply of oxygen in the blood could be offset by increasing amount of hemoglobin (red blood cell) to improve oxygen delivery (26). This is one of the best-known features of acclimation to high altitude. However, there is a downside: when there is too much hemoglobin, excessive polycythemia occur, and CMS may develop (7). The excessive polycythemia increases blood viscosity, and increase blood flow resistances through the lung capillary. The increased cardiac output, together with the increased resistance may lead to pulmonary hypertension, causing cor pulmonale (right-heart failure) (27). The complex interaction of the respiratory and hematologic changes can also induce the appearance of neurological symptoms, which include sleep disorders, headache, dizziness, and mental fatigue.

2.4 CMS associated factors

Comparing the prevalence of CMS from most of the world's high altitude regions show a markedly lower prevalence among Tibetans than in Han or Andeans at similar altitude (28). However, information about the prevalence of CMS is lacking for the Rocky Mountain region.

2.4.1 Altitude

The prevalence of CMS increases progressively as altitude increases. At 2260 to 2800m, the prevalence of CMS is 0 % in Tibetan and 1.1% in Han Chinese, at 3050 to 3800 m it is 0.6% in Tibet and 5.4% in Han Chinese, at 4000 to 5200 m it is 2.3 % in Tibetan, 7.9% in Han Chinese and 12.2% in Peruvians (1). At altitude below 3000 m above sea level CMS is uncommon and rarely occurs, even among longtime residents (15). It also found (29) the prevalence of CMS in young soldiers who had relatively short time (9-21 months) at 5,000 m to be 30.43% compared with 9.33% in the Chinese troops in Lhasa (at 3,700 m).

2.4.2 Hemoglobin concentrations

In high altitude dwellers, hemoglobin concentrations may raise compare with lowlanders, to help the oxygen transport. The increased hemoglobin concentrations in high-altitude dwellers is a double-edged sword. Too low hemoglobin concentrations gives too little oxygen to the cells, but if the increase is too high (excessive erythrocytosis) CMS may develop. The prevalence of excessive polycythemia is reported in three different altitudes in Tibet among Han Chinese migrants and native Tibetans older than 15 year: in Lhasa (3,700m) it is 13.0 % in Han Chinese male workers and 1.1 % in native Tibetan male workers; 1.6 % in Han Chinese female workers and 0 % in native Tibetan female workers; in Gyangze (4,040m) it is 31.5 % in Han Chinese male workers and 4.8 % in native Tibetan male workers; 3.8 % in Han Chinese female workers and 0 % in native Tibetan female workers; in Negchu (4,500-4,700m) it is 38.4 % in Han Chinese male workers and 14.4 % in native Tibetan male workers, 7.2 % in migrants female workers and 6.5 % in native Tibetan female workers (1). Tibetans appear to exhibit a reduced erythropoietic response to hypoxia compared to Andeans (30;30;31) and Western sojourners (32). Both in Tibetan and Han Chinese children, the hemoglobin concentrations is higher in high altitude residents compared to low altitude, and show little difference with gender and ethnicity before puberty (33). In a study from Southern Peruvian Andes among children aged 1-15 years the hemoglobin concentrations increases from 15.9 ± 1.1 g/dl at 4355 m to 17.6 ±1.1 g/dl at 5500 m, i.e, a 11% increase, in adults aged 40-60 years the increase is 9.6% (18.0±1.1g/dl vs.19.3 ± 1.2 g/dl) at same altitude, and the differences in the concentration between gender can only be seen after puberty (34).

2.4.3 Arterial oxygen saturation

The altitude has inverse relation with Arterial oxygen saturation (SaO_2). It is reported that SaO_2 decrease with increasing altitude both in Tibetan and Han Chinese boys 13-16 years old, with no ethnic difference, at an altitude of 3417 m, the SaO_2 was 89.7% in native Tibetan boys and 89.2% in Han Chinese boys, at 4300 m, the values were 88.5% and 87.2%, respectively (35). Likewise, that SaO_2 values of Han Chinese men (88.6%) who had migrated to 3700 m (Lhasa) during childhood were similar to those of native Tibetan men (89.3%) who have lived in Lhasa all their lives (36). In a study from central Tibet at an altitude of 3800-4200 m, it is reported that mean SaO_2 values increase from approximately 87% to 89.3% between 5 and 11 year of age; but from ages 11 through 19 year, there are only minor fluctuations in mean saturation values (37). The hemoglobin concentrations value of 17.5 g/dl and SaO_2 of approximately 87% has been suggested as the optimal limit for effective oxygen transport in adult altitude residents (27). The left-shift dissociation curve position can increase hemoglobin-oxygen affinity and raise SaO_2 at a given PO_2.

2.4.4 Hypoxic ventilatory response

Studies on high altitude inhabitants indicate that there is a gradual attenuation of ventilatory sensitivity to hypoxia with increasing years of residence (38). Lifelong high-altitude residents of North and South America acquire blunted hypoxic ventilatory responses (HVR) and exhibit decreased ventilation compared with acclimatized newcomers (36). Tibetans have similar HVR with lowlanders, both at high altitude and sea level (39). In a study comparing Tibetan with Han Chinese long-term immigrants at 3,700 m (Lhasa), the Tibetans had higher HVR values than the Han Chinese, and showed little decline with age. Among the Han subjects, HVR decreased with length of living at high altitude (36). The HVR in Tibetans is roughly double that of Bolivian Aymara at similar altitude (40), one can therefore speculate that Tibetans are better adapted to high altitude, which is also indicated by a lower prevalence of CMS than among Aymara. Persons with CMS have lower levels of ventilation and a greatly diminished HVR compared with normal residents of high altitude (41). In Bolivia, a study among young CMS patients (age<30 yr) showed that there is moderate attenuation of HVR, and among older CMS patients (age>30 yr) the magnitude of response was even more attenuated (13). Thus, suggesting that diminished HVR may have an important relationship with CMS.

2.4.5 Lung function

It seems more and more evident that excessive erythrocytosis results from some respiratory or ventilatory alterations (6). Ventilation measured in CMS patients has repeatedly been found to be low as compared with healthy individuals (11). It is reported a prevalence of excessive erythrocytosis as high as 32.4% in cases with lung diseases in Cerro de Pasco at 4340 m (42). In La Paz the over-all hospital frequency of excessive erythrocytosis is 28%, with most of their excessive erythrocytosis patients diagnosed with a respiratory disease (43). A study comparing Tibetan and Han Chinese adolescents between 13 and 16 years of age at altitudes of 3417 m and 4300 m, showed that the FEV_1 value at 3417m is 3.01 ± 0.14L for Tibetan and 2.44 ± 0.13L for

Chinese; at 4300 m, the FEV_1 is 3.16 ± 0.16L for Tibetan and 2.61 ± 0.13L for Han Chinese, indicating that the Tibetans had significantly higher lung function than Han Chinese (35). Another study compares native Tibetan with the Han Chinese immigrants show that chest circumference was greater in the Tibetans than in the Han subjects (85 ± 1 vs 82 ± 1 cm, $P < 0.05$), furthermore that Tibetans have a larger vital capacity than the Han subjects (5.00 ± 0.08 vs 4.51 ± 0.10 L, $P < 0.05$) (44). This may be important for better lung capacity and preserving arterial oxygen saturation when living at a high altitude. It is reported that the FVC and FEV_1 were significantly higher in healthy native highlanders of Ladakh compared to healthy acclimatized lowlanders [FVC: 5.02 (0.51) vs. 3.89 (0.45) L, $p < 0.0001$; FEV_1: 4.27 (0.47) vs. 3.44 (0.37) L, $p < 0.0001$] at an altitude of 3450 m in the western Indian Himalayas (45). It is found that the isolated racial group of Himalayan Sherpas resident at an altitude of 3840 m, the adults aged from 18-78 years, show FEV_1 of 2.78 L in female and 3.88 L in male; the FVC of 3.40 L in female and 4.70 L in male. While in children aged 8-17 years the FEV_1 is 2.72 L in girls and 3.09 L in boys, the FVC is 2.99 L in girls and 3.48 L in boys (46) These lung function values are significantly larger than predicted, based on equations for the European Coal and Steel Community for adults (47) and Caucasian reference values for children (48). From this study, one can speculate that this is an adaptation in response to chronic hypoxia. In Quechua males living in the area around the city of Huancavelica at 3,680 m or higher, the FVC was between 3.1–6.9 L; and FEV_1 was between 2.4-5.7 L, and found strong negative correlation of both FVC and FEV_1 with age (16).

It is reported (49) that indigenous populations of the Tibetan and Andean plateaus exhibit 4 quantitative traits which provide evidence of different adaptive responses to high altitude hypoxia. These 4 traits are: resting ventilation, hypoxic ventilatory response, oxygen saturation and hemoglobin concentration. We did not test resting ventilation and hypoxic ventilatory response, but lung function can also reflect resting ventilation indirectly. To our knowledge, there is no study with sufficient sample size which has measured lung function among 9-10 year old children living in Tibet.

2.4.6 Gender

The prevalence of CMS and excessive erythrocytosis is higher in men than in women. It has been found in Bolivian Andeans that CMS was predominant in males of a mixed or entirely European ethnic background (50). In Cerro de pasco Peru (at 4,300 m), the prevalence of excessive erythrocytosis is 15.6% for male and 8.8% for female. In that study the female sample was divided into postmenopausal and premenopausal groups for comparison, and found 45% of the postmenopausal subjects presented a high CMS score, whereas only 22% of the premenopausal subjects presented high score (51). Several factors may be responsible for this sex difference. In pre-menopausal women, menstrual blood as a 'natural phlebotomy' may prevent marked erythrocytosis (15). It is also possible that the better oxygenation and lower Hb levels in women with long residing at high altitude is associated with higher levels of the female sex hormones progesterone in the luteal phase of the cycle (52). Therefore menopause may represent a contributing factor for the development of CMS.

2.4.7 Age

A study of Andean health high altitude miners in Cerro de pasco (4340 m) shows that excessive erythrocytosis prevalence increases with age: 6.8% at age 20-29; 15.4% at age 30-39; 18.8% at age 40- 49; 27.4 % at age 50-59 and 33.7% at age 60-69 (53). Boliva highlanders show CMS signs more frequently and more severe symptoms with old age (>30 years) than young age(<30 years) (54).

2.4.8 Ethnicity

CMS has been reported most commonly in Quechua and Aymara Indians living in the Andes (55). The prevalence of CMS is estimated to be 15% in Quechuan Andeans and 5.6% in Han Chinese and 1.2% in Tibetans at similar altitudes (50). Tibetans have higher SaO_2 and lower Hb in comparison with Han Chinese immigrants and Andean natives. Tibetans also have greater ventilatory capacity and HVR as well as greater physical performance (15).

2.4.9 Obesity

A high body weight has been suggested to be an additional risk factor in the development of CMS, it seems to play a role in lowering arterial oxygen saturation, and thus producing excessive erythrocytosis (42). At high altitude, men with excessive erythrocytosis have been found to have higher body weights when compared with men with physiologic erythrocytosis (53). Obese persons appear to have higher pulmonary hypertension than normal subjects at the same altitude. It is also reported that obese persons working at altitudes above 4000 m for 3 to 5 months lose weight, reaching near normal body weights (56). It appears that minor obese individuals are at no particular disadvantage at high altitudes. For moderate obese individuals without cardiopulmonary disease, some caution seems appropriate. Grossly obese persons should probably not go to high altitudes (56).

2.5.0 Smoking

It is well known that respiratory abnormalities are caused by the habit of smoking cigarettes. Therefore, it is easy to think that smoking is associated with the development of CMS. A study shows that the prevalence of CMS in Han men is three times higher in smokers than in non-smokers (15). The mechanism of the association is unknown, but it could be through the effect of the production of accentuated hypoxemia, centrilobular emphysema and thus reducing alveolar ventilation.

2.5.1 Occupation

It is interesting to note that professionals show a CMS prevalence which is two to three times that of farmers and herders within Tibetan and Han Chinese, both in male and female (15). With the rapid development of modern cities nowadays, more and more high altitude regions become urbanized or industrialized. Thus, the high altitude residents will be at higher risk of developing CMS.

3 Aim and research objectives

The ***aim*** of the present study is to give descriptive data regarding lung function, hemoglobin concentration, and arterial oxygen saturation in sub-groups of native Tibetan and Han Chinese children living in Lhasa at 3700 meters above sea level and native Tingri Tibetan children living in Tingri at 4300 meters above sea level. The selected factors may increase the risk of later development of CMS. In this thesis, emphasis will be put on lung function measures.

The ***specific objectives*** are to compare 9-10 year old children living at an altitude of 3,700m (Lhasa native Tibetan and Han Chinese) and 4,300m (Tingri native Tibetan) with respect to lung function (FEV_1, FVC, FEF_{50}), hemoglobin concentration, and arterial oxygen saturation.

4 Hypotheses

Our hypotheses are that lung function values FEV_1,FVC and FEF_{50} are better in Lhasa Tibetan children than in Tingri Tibetan children and lowest among Han Chinese children. Furthermore, that the hemoglobin concentration is highest among Tingri Tibetan children, followed by Lhasa Tibetan children and Lhasa Han Chinese children. Finally, we hypothesize that the arterial oxygen saturation is lowest among Tingri Tibetan children, followed by Han Chinese children and Lhasa Tibetan children.

CHAPTER II

MATERIAL AND METHODS

II Material and Methods

1 Design for present study

1.1 Study design

Two cross sectional studies were conducted at 3700 meters (Lhasa) and 4300 meters (Tingri) above sea level.

1.2 Study area

The data of the present thesis was collected in Lhasa city in 2005 and in Tingri County in 2007. The capital city of Tibet Autonomous Region (TAR), Lhasa, is located on the North bank of the Kyichu River (Lhasa River), the sub branch of Yarlung Tsangpu River. The city was settled 1,300 years ago, and covers 30,000 square kilometers; the elevation is 3,700 meters above sea level. Its average yearly temperature is 8.5 ^{0}C, and has 3,021 hours of sunlight annually (57). Lhasa has acted as the centre of Tibet politics, economy, culture, transport as well as a sacred place of Tibet Buddhism.

Tingri County belongs to Shigatse District which is one of the Tibet's six prefectures. It is situated at the foot of the Mount Everest, in the middle of the Himalayas. The average altitude of Tingri where the data was collected is 4300 meters above sea level. Its annual average daily temperature is 0.7 ^{0}C. There are several mountains in Tingri, four of them are over 8000 meters: Mount Lhotse, Mount Cho Oyu, Mount Makarluh and Mount Everest. Tingri County has a total area of 14,000 square meters and is located 244 kilometers away from the the Shigatse prefecture (58).

2 Subjects

2.1 Population

The total population in Lhasa municipality is 420,827, 81.6% are Tibetans and 17.0% are Han Chinese (57). The Lhasa data was collected in 2005 from 9 randomly selected schools in Lhasa, and includes 812 schoolchildren (406 Tibetan and 406 Han Chinese) aged 9 to 10 years. We used the same methods to collect data in Tingri in 2007. The data from Lhasa, except lung function data, is published as a part of an M.Phil thesis in 2006 (18), and more details regarding methodology can be found. The “method” section in the present thesis will focus on the Tingri data collection.

Tingri County has approximately 46,000 inhabitants, and almost all of them are Tibetans. The population density is 3.3 people per square kilometer. The whole county has one primary school in the county center and 13 primary schools in the villages (59). The study sample included 444 (225 boys and 219 girls) 9 ~10 year old students randomly selected from 5 primary schools which again were randomly selected from 14 primary schools.

Inclusion criteria

-- Lhasa Tibetan or Han Chinese Living in Lhasa city, and Tingri Tibetan living in Tingri county, who were on school lists in Primary Schools.

--boy or girl, born between 1^{st} of January and 31^{st} of December nine or ten years old at the time of the data collection.

Exclusion criteria

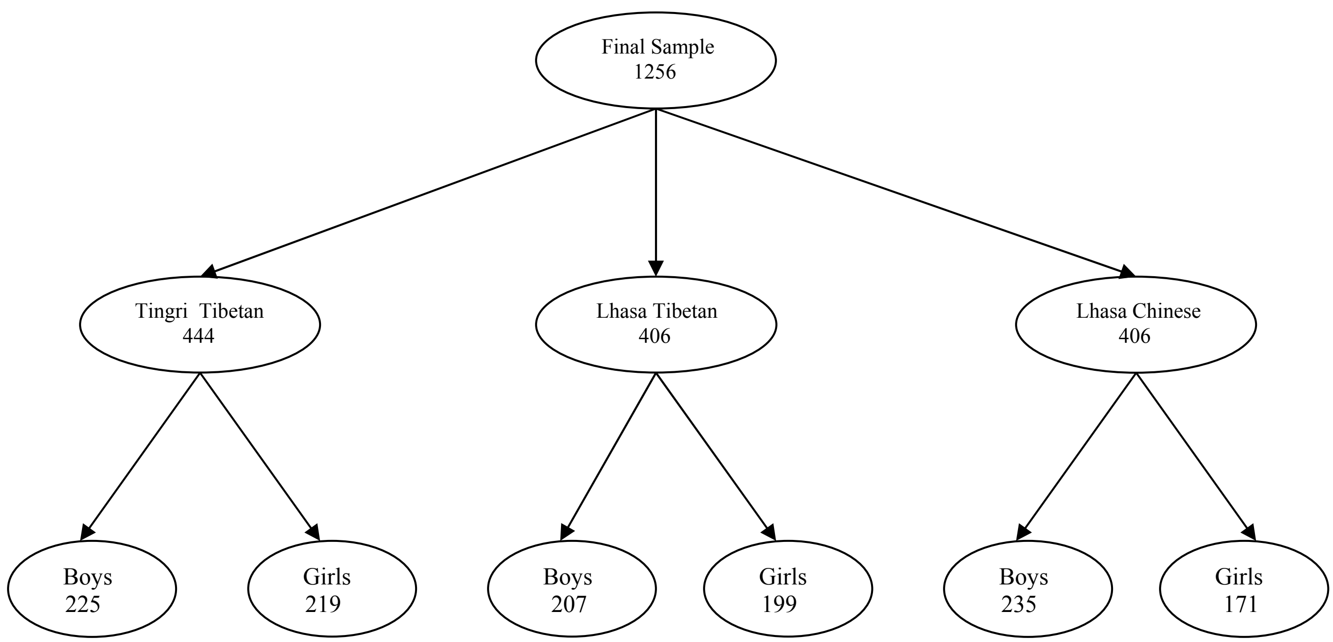
--Suffering from illnesses, diseases or injuries which made it impossible to complete the test.

2.2 Sample size calculation

In order to determine the required sample size for the present study, we consider comparison of lung function between children living at the two altitudes as a central research question, thus, we calculated the sample size necessary to address this question. We used the colleted data from Lhasa, the standard deviation for lung function FEV_1 which was 0.26 (assumption based on figures from lung function measured among 406 Tibetan children aged 9 to 10 years old in Lhasa). The subjects needed in each group were calculated according to the MedCalc statistical program (made in Belgium). With a power of 0.90 (beta), a significance level of 0.05 (alpha), and aiming at being able to show a difference in FEV_1 of 0.10 as statistical significant, the necessary sample size in each group is 143. Thus, all students in 5 randomly selected schools would give approximately 500 students, allowing for separate analysis by sex and sub-group analysis, and allow for drop outs.

2.3 Sampling method

Random sampling method has been used to select the study sample. Random selection procedure will ensure that each unit of the sample is chosen on the basis of chance, all units of the study population will have an equal chance of being included in the sample. We wrote down names of schools on a piece of paper, the puckered papers were put into a box, mixed together, and randomly selected 5 out of 14 (one primary school in the county centre, and 13 primary schools in the villages). One teacher from each of the selected schools prepared a list of all 9 to 10 year old students. The lists included 490 students, we decided to include all on the lists, 30 students did not fulfil the criteria for age and were therefore excluded, 16 students did not go to school at the days of data collection and none of the other students refused to participate. Thus, 444 (97%) Tingri children (219 girls and 225 boys) were included in the final sample. The same to Lhasa children, 9 primary schools were randomly selected from Lhasa, 817 students were included in the lists, however, 5 students were unable to participate, only one because of refusal. Thus, 812 (99%) Lhasa children were participated in the study. 406 Lhasa Tibetan children (207boys and 199grils) and 406 Lhasa Han Chinese children (235 boys and 171 girls) were randomly selected. Thus, a total of 1256 children participated in this study. However, SaO_2 and HR were measured in only 90 boys and 65 girls of the Tingri Tibetan children, because the others were too low to complete the bicycle test, which was not the part of present study but did test with SaO_2 and HR measurements.



3 Data collection (Tingri)

In order to provide easy access for participants, one study room was rented in each school during the data collection. Lung function, anthropometric measurement, hemoglobin concentration, arterial oxygen saturation, and standard individual questionnaires were conducted through one month from 26th September to 26th October in 2007. After this data collection, we checked the lung function curves, and most of them did not fulfil the quality of criteria (60). Because of poor quality of lung function data, all students were tested again during one week from 16th to 23rd in December 2007. All data were carefully collected by specially trained and experienced field workers using standardized methods and stringent level of quality control according to the protocol.

3.1 Training of field workers

Two Tibetan PhD students Bianba and Yangzom, Section from preventive medicine and Epidemiology, University of Oslo and two second year students at the Medical college of Tibet University, in addition to the M.phil student, GongGaLanZi, took part in the data collection. They were all Tibetan, able to speak and write the Tibetan and Chinese languages and had a medical background. They were familiar with the protocol in detail and trained in basic research methods and in all practical aspect related to the current project.

3.2 Pilot study

Pre-testing was done in order to identify potential problems for improving the quality of questionnaires and the data collection process. We tested 10 pupils aged 9-10 years with the whole research team to find any changes necessary before printing of questionnaire and carrying out the study.

In order to check whether the filed workers were sufficiently comprehended, all questions in the questionnaires were asked to the same informant with all field workers present. The field workers recorded answers to all questions, and any differences were discussed and some adjustments in the questionnaire were performed. The questionnaires have also been checked by whether the informants give a valid answer or not. After completion of questionnaires, the participants were rechecked by the principal researcher whether they understood the question as clearly as it was meant to be.

Through the pilot study, anthropometric measurements, hemoglobin concentration measurement, arterial oxygen saturation measurement and lung function test were tested out within the 10 individuals to check how long it took to perform whole procedure with one pupil, the correct operation of equipment and reliability of the results when instruments or test were administered by different members of the research team.

We modified all revealed problems and discussed how to improve our study with all team members after the pilot study to make sure that the data should be valid for incorporation into the main study.

4 Methods

4.1 Anthropometrics

The anthropometric measurements include body weight, height and chest circumference. The weight was measured without shoes and in underwear to the nearest 0.1 kg, using electronic weight scale (OMRON, HN-281). Height was measured to the nearest 0.5cm (TZG, Shanghai, china). Chest circumference was measured at a point crossing both nipples to the 0.1 cm with subjects standing and breathing normally.

Body mass index (BIM) was calculated as weight divided by height squared [(kg)/height (m) ^{2}]. Following the criteria of international cut-off points for body mass index for thinness, overweight and obesity by sex for exact ages between 2-18 years (61;62), BMI was operationalized to: thinness: ≤ 14.49 (boy) and ≤ 14.43 (girl); normal:14.50-19.45 (boy) and 14.44- 19.44 (girl); overweight: 19.46-23.38 (boy) and 19.45-23.45 (girl); obesity: ≥ 23.39 (boy) and ≥ 23.46 (girl).

4.2 Lung function

Lung function test was performed with Spiro USB (Micro Medical Limited, Rochester, Kent,UK). It was assessed by measuring Forced expiratory volume in 1 seconds (FEV_1), Forced vital capacity (FVC) and Forced expiratory flow 50% (FEF_{50}). Measurements were made with the subject sitting with the backing in upright position and the feet on the floor, and attach with nose clip, with the mouthpiece in mouth and closed lips around the mouthpiece. The subject breathes steadily three to four times. Then the subject inhales rapidly and completely, followed by maximal force expiration where the subject expires as fast, hard and long as possible. Exhale maximally until no more air can be expelled while maintaining an upright posture. The subjects was explained orally and visually how to complete the test by field workers. They have repeated instructions if necessary, coaching vigorously. Participants practice until they were able to do the test in the correct way. All students made between 3-8 tests, and all were checked visually by 2 trained researchers (papers printout of lung function curves with values) and deleted if they did not fulfill the following criteria (60): 1. without an unsatisfactory start of expiration, characterized by excessive hesitation or false start extrapolated volume or EV > 5% of FVC or 0.150L, whichever is greater; 2. Without coughing during the first second of the manoeuvre, thereby affecting the measured FEV_1 value, or any other cough that, in the field workers, judgment, interferes with the measurement of accurate results; 3. Without early termination of expiration; 4. Without a Valsalva manoeuvre or hesitation during the manoeuvre that causes a cessation of airflow, which precludes accurate measurement of FEV_1 or FVC, 5. without a leak, 6. without an obstructed mouthpiece (e,g. obstruction due to the tongue being placed in front of the mouthpiece, or teeth in front of the mouthpiece); 7. Without evidence of an extra breath being taken during the manoeuvre. The acceptable curves were determined after meeting all the seven conditions mentioned above, then, the one best (largest) values for each of FEV_1, FVC, and FEF_{50} were selected, and used in the analyses. According to the criteria (60) of lung function curve, we excluded 10 Tingri Tibetan children 4 Lhasa Tibetan children and 5 Lhasa Han Chinese children 's data, and we missing 38 Tingri Tibetan children, 5 Lhasa Tibetan children and 4 Lhasa Han Chinese children's data.

Finally, lung function data with 396 (195 boys and 201 girls) Tingri Tibetan children 397 (204 boys and 193 girls) Lhasa Tibetan children and 397 (233boys and 164 girls) Lhasa Han Chinese children were available for analysis.

4.3 Hemoglobin concentration

The [Hb] was performed using the HemoCue Hb 201^+ analyzer (Ångelholm, Sweden). We chose ring finger to be punctured using a lancet. Applying pressure towards the fingertip until a drop of blood appears, wipe away the first 2 drops of blood with gauze. Re-apply pressure until another drop of blood appears. When the blood drop is large enough, fill the microcuvette in one continuous process. Wipe off excess blood from the outer surface of the Cuvette with paper towel, being careful not to touch the open end of the Cuvette. Then place the filled cuvette in the Cuvette holder. And the result was displayed automatically. We calibrated the analyzer in the morning before the testing every day using the HemoCue Hemoglobin calibrator (12.0±0.2).

4.4 Arterial oxygen saturation

The arterial oxygen saturation was measured using the Nellcor NPB-40 (California,USA) handheld pulse oximeter. OXI-P/I OxiBand was applied for children less than 40 kg and DURASENSOR DS-100A for children above 40 kg, respectively. The surface of the sensor and subject's finger has been cleaned with 70% isopropyl alcohol. Then attached sensor around the index finger. Children have to lie down for 2-3 minutes before the measurement and then resting arterial oxygen saturation (SpO_2 rest) was recorded.

4.5 Heart rate

The heart rate was measured by a heart rate sensor (Polar Electro OY, Kempele, Finland) which was attached above the processus xiphoideus. And the same measurement procedure was used for arterial oxygen saturation.

4.6 Questionnaire

The questionnaire include question about demographic characteristic, parental smoking, diet, socioeconomic factors and physical activity, modified after ISAAC—and WHO questions (63) (these data were not include in the present thesis, except parental smoking).

In order to check the internal validity of the questionnaires, questionnaires have been translated from English into Chinese and Tibetan and translated back in English to investigate if there were any differences. The questionnaire was completed by the pupils under the supervision of field workers.

5 Data management

All preparation work has been done before the field work, which includes printing, binding and coding the questionnaires and calibrating the equipments. The accuracy of the complete questionnaires and the results of physical examination were checked every day after data collection in the fieldwork. The responses were coded and the data was entered to a laptop computer using the Statistical Package for Social Science (SPSS 12.0 version).

6 Data analysis

The Statistical Package for Social Scientists (SPSS 14.0 version) was used for statistical analyses. Descriptive analyses were used for describing means, standard deviations (SD) and/or 95% confident interval (CI). For testing of differences in height, weight, Heart rate, SaO_2 and [Hb] between three groups (Tingri Tibetan, Lhasa Tibetan and Lhasa Chinese), ONE-WAY ANOVA for continuous outcome was used. Chi-square (χ^2) tests were applied for comparing differences in categorical variables e.g: the prevalence of thinness, normal weight, over weight, obesity and parental smoking. Analyses of covariance (ANCOVA) was used for comparing differences in lung function among children in three different groups: Tingri Tibetan, Lhasa Tibetan and Lhasa Han Chinese. Level of statistical significance was set to $P < 0.05$.

7 Ethical considerations

The subjects participated in this study voluntarily. The participants and their teachers were informed about the aims, method and procedure of the study, and they also informed that participants have the right to abstain from participation in the study or to withdraw consent to participate at any time for any reason without any consequence. The subjects were not participating in any procedures which may do potential harm to them. All information about the subjects was handled confidentially.

The research protocol was approved by the Health Bureau of Tibet Autonomic Region (TAR). The Medical College of Tibet University was responsible for data collection and field work according to local standard and legislation, and ensured that it was based on informed consent. The collected data was stored at the University of Tibet according to local rules. Data entry was conducted at the University of Tibet and data have been brought to Norway. The Norwegian supervision would be restricted to the planning of the study, scientific supervision, data analyses, and reporting.

CHAPTER III

RESULTS

1 Anthropometrics

The gender specific anthropometrical characteristics of Tingri Tibetan children, Lhasa Tibetan children and Lhasa Han Chinese children are illustrated in table1.

All anthropometrical measurements were statistical significantly higher in Lhasa Tibetan Children than Tingri Tibetan children. Lhasa Chinese did also have higher anthropometrical measurements than Tingri Tibetan children.

At the same altitude, all anthropometrical measurements were statistical significantly higher in Lhasa Tibetan Children than Lhasa Han Chinese children. There were no gender differences within the ethnic groups within the same altitude.

Only a small proportion of the children were overweight, between 0.5-4.8 % in the different subgroups (Table 2). However, thinness is common from 36.7% in Tingri Tibetan girls to 14.0% in Lhasa Tibetan boys.

Table 1 Anthropometrical characteristic of 9-10 years old Tingri Tibetan children, Lhasa Tibetan children and Lhasa Han Chinese children.

	Boys						Girls					
	Tingri Tibetan (N 225)		Lhasa Tibetan (N 207)		Lhasa Chinese (N 235)		Tingri Tibetan (N 219)		Lhasa Tibetan (N 199)		Lhasa Chinese (N 171)	
	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D
Age (years)	9. 6*	0. 5	9. 8	0. 4	9. 9△ △	0. 3	9. 6**	0. 5	9. 8	0. 4	9. 9△ △	0. 3
Weight (kg)	22.4**	2. 5	29.7 O O	5. 3	27.8△ △	5. 1	22.4**	2. 8	29.4 O O	5.1	27.6△ △	5. 2
Height (cm)	122.1**	5. 4	134. 8 O	5. 4	133. 5△ △	6. 4	122. 8**	6. 3	135. 9 O	6. 7	133.7△ △	6. 6
BMI (kg/m2)	15.0**	1. 0	16.2 O O	2. 1	15.5△	1. 8	14.8**	1. 1	15.8 O	1. 8	15.4△	1. 9
Chest (cm)	59.8**	2. 6	64.7 O O	4. 7	61.8△ △	4. 3	58.9**	2. 9	63.7 O O	4. 6	61.3△ △	4. 5

* p < 0. 05 Tingri Tibetan VS Lhasa Tibetan, ** p < 0. 001 Tingri Tibetan VS Lhasa Tibetan.

△ p < 0. 05 Tingri Tibetan VS Lhasa Chinese, △ △ p < 0. 001 Tingri Tibetan VS Lhasa Chinese.

O p < 0. 05 Lhasa Tibetan VS Lhasa Chinese, O O p < 0. 001 Lhasa Tibetan VS Lhasa Chinese.

Table 2 The percentage of thinness, normal weight, overweight and obesity among 9-10 years old Tingri Tibetan children, Lhasa Tibetan children and Lhasa Han Chinese children.

	Boys				Girls			
	Tingri Tibetan	Lhasa Tibetan	Lhasa Chinese	p-value	Tingri Tibetan	Lhasa Tibetan	Lhasa Chinese	p-value
Thinness (%)*	31.1	14.0	27.4		36.7	20.2	33.7	
Normal (%)*	68.4	79.7	68.8	0.000	63.3	75.8	62.7	0.002
Overweight (%)*	0.5	4.8	3.4		0	3.5	3.0	
Obesity (%)*	0	1.4	0.4		0	0.5	0.6	

* **Based on BMI operationalized according to internationally accepted criteria (61;62).**

Missing information varied between 2 and 36 for each of the item.

2 Parental smoking habits

Smoking is more common in Lhasa than in Tingri, and more common among Han Chinese than native Tibetan (Table 3). As many as 85.6% of Lhasa Chinese children reported smoking inside the home, as compared with 79.1% in Lhasa Tibetan and 47.3% in Tingri Tibetan homes (Table 3).

Table 3. Prevalence of household smoking habits reported by Tingri Tibetan children, Lhasa Tibetan children and Lhasa Han Chinese children aged 9-10 years.

	TingriTibetan n (%)	LhasaTibetan n (%)	LhasaChinese n (%)	P-value
Does your mother smoke				
Formerly	8 (1.9)	22 (5.5)	21 (5.2)	<0.05
Currently	7 (1.6)	14 (3.5)	12 (3.0)	0.22
Does your father smoke				
Formerly	212 (49.1)	247 (62.5)	271 (68.1)	<0.001
Currently	206 (47.7)	233 (59.6)	253 (62.8)	<0.001
Anyone smoke in your home	204 (47.3)	317 (79.1)	345 (85.6)	<0.001

Missing information varied between 2 and 15 for each of the item

3 Hemoglobin concentration

Both Tingri Tibetan boys and girls had lower haemoglobin concentration than Lhasa Tibetan boys and girls, respectively ($p<0.001$), and Lhasa Han Chinese boys and girls, respectively ($p<0.001$) (Table 4). In Lhasa, both native Tibetan boys and girls had lower ($p<0.001$) haemoglobin concentration than Han Chinese.

In Tingri Tibetan, the hemoglobin concentration at tenth percentiles were 12.5g/dl for boys and 12.6g/dl for girls, and ninetieth percentiles were 15.5g/dl for boys and 15.4g/dl for girls; as compared with Lhasa Tibetan children: 13.0g/dl for boys and 13.1g/dl for girls at tenth percentile, 16.3g/dl for boys and 16.2g/dl for girls at ninetieth percentile, and with Lhasa Han Chinese: 13.7g/dl for boys and 13.7g/dl for girls at tenth percentile, 16.9g/dl for boys and 16.9g/dl for girls at ninetieth percentile (figure 1 and figure 2). There were no gender differences in Tingri Tibetan, Lhasa Tibetan and Lhasa Han Chinese children (Table 4).

Table 4. Haemoglobin concentration (g/dl) in Tingri Tibetan, Lhasa Tibetan and Lhasa Han Chinese 9 to 10 year old School children.

	Boys			Girls		
	n	mean	95% CI	n	mean	95% CI
Tingri-Tibetan	207	14.0^{**}	(13.8-14.1)	196	14.0^{**}	(13.8-14.2)
Lhasa-Tibetan	206	14.6^{oo}	(14.4-14.8)	199	14.6^{oo}	(14.5-14.8)
Lhasa-Chinese	233	$15.3^{\triangle\triangle}$	(15.1-15.5)	169	$15.4^{\triangle\triangle}$	(15.2-15.6)

		Boys			Girls		
	Years of living in Tibet	n	mean	95% CI	n	mean	95% CI
Lhasa-Chinese	≤3 yrs	80	15.3	(15.1-15.6)	64	15.2	(14.9-15.5)
	4-5 yrs	49	15.5	(15.2-15.9)	33	15.6	(15.2-15.9)
	6-7 yrs	27	15.2	(14.8-15.7)	24	15.8	(15.3-16.3)
	8-10 yrs	45	15.3	(14.9-15.6)	31	15.1	(14.7-15.6)

** $p < 0.001$ Tingri Tibetan VS Lhasa Tibetan. $^{\triangle\triangle}$ $p < 0.001$ Tingri Tibetan VS Lhasa Chinese. ^{OO} $p < 0.001$ Lhasa Tibetan VS Lhasa Chinese.

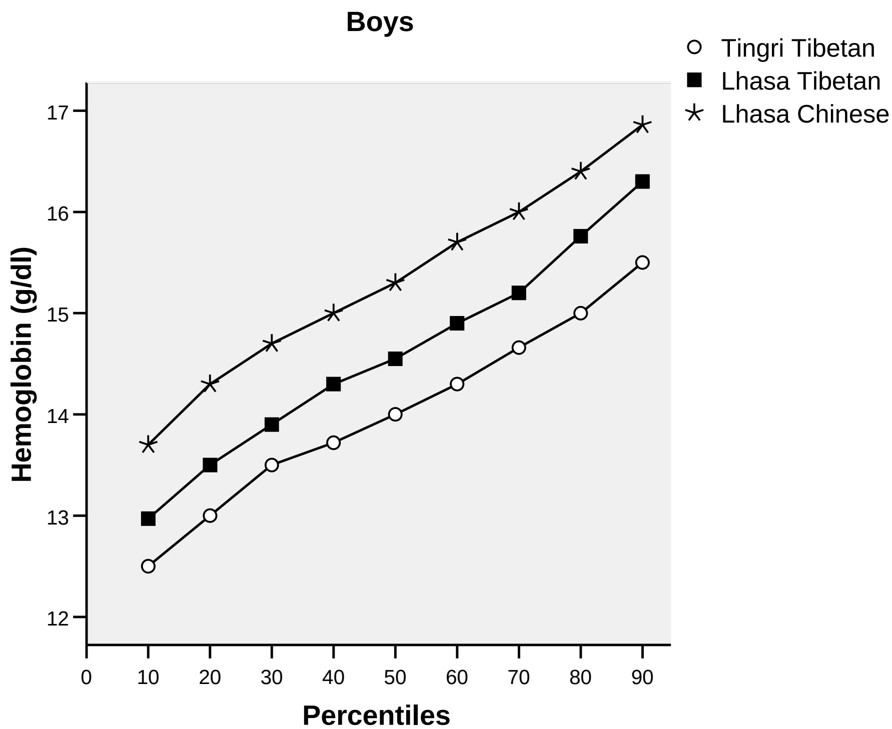


Figure 1. Haemoglobin concentration in 9-10 year old Tingri Tibetan, Lhasa Tibetan and Lhasa Han Chinese boys by percentiles.

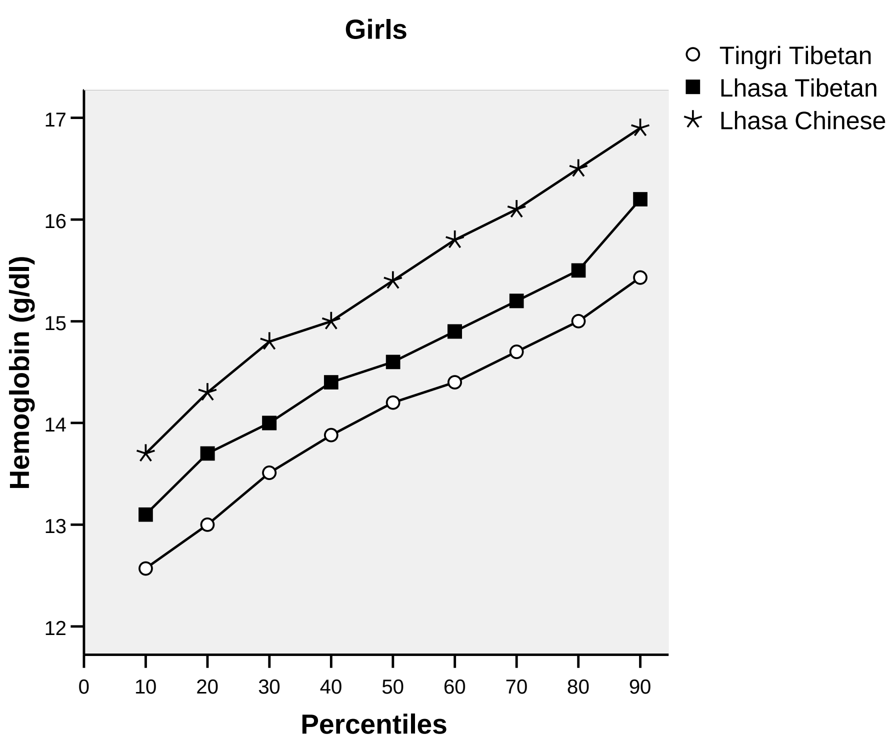


Figure 2. Haemoglobin concentration in 9-10 year old Tingri Tibetan, Lhasa Tibetan and Lhasa Han Chinese girls by percentiles.

4 Heart rate at rest (HR rest) and arterial oxygen saturation at rest (SaO_2 rest)

There were no differences between Tingri Tibetan, Lhasa Tibetan and Lhasa Chinese in heart rate at rest (Table 5). Both native Tingri Tibetan boys and girls had significantly lower arterial oxygen saturation than Lhasa Tibetan and Lhasa Han Chinese boys and girls respectively (Table 5, Figure 3 and Figure 4).Lhasa Tibetan girls had higher arterial oxygen saturation than Chinese girls ($p<0.05$).

Table 5. Mean heart rate at rest (HR rest) and arterial oxygen saturation at rest (SaO_2 rest) in Tingri Tibetan, Lhasa Tibetan and Lhasa Chinese 9 to 10 year old school children.

		Boys			Girls		
		n	mean	95% CI	n	mean	95% CI
HR_{rest}	Tingri-Tibetan	90	86	(84-89)	65	87	(84-90)
	Lhasa-Tibetan	200	87	(86-89)	183	89	(87-91)
	Lhasa-Chinese	217	89	(88-91)	141	89	(87-91)
$SpO_{2\ rest}$	Tingri-Tibetan	90	86.9^{**}	(86.1-87.6)	65	87.7^{**}	(86.9-88.5)
	Lhasa-Tibetan	200	91.0	(90.6-91.4)	183	91.1^{o}	(90.7-91.5)
	Lhasa-Chinese	217	$90.5^{\triangle\triangle}$	(90.1-91.0)	141	$90.2^{\triangle\triangle}$	(89.6-90.7)

* $p < 0.05$ Tingri Tibetan VS Lhasa Tibetan, ** $p < 0.001$ Tingri Tibetan VS Lhasa Tibetan.

$^{\triangle}$ $p < 0.05$ Tingri Tibetan VS Lhasa Chinese, $^{\triangle\triangle}$ $p < 0.001$ Tingri Tibetan VS Lhasa Chinese.

^{O} $p < 0.05$ Lhasa Tibetan VS Lhasa Chinese, ^{OO} $p < 0.001$ Lhasa Tibetan VS Lhasa Chinese.

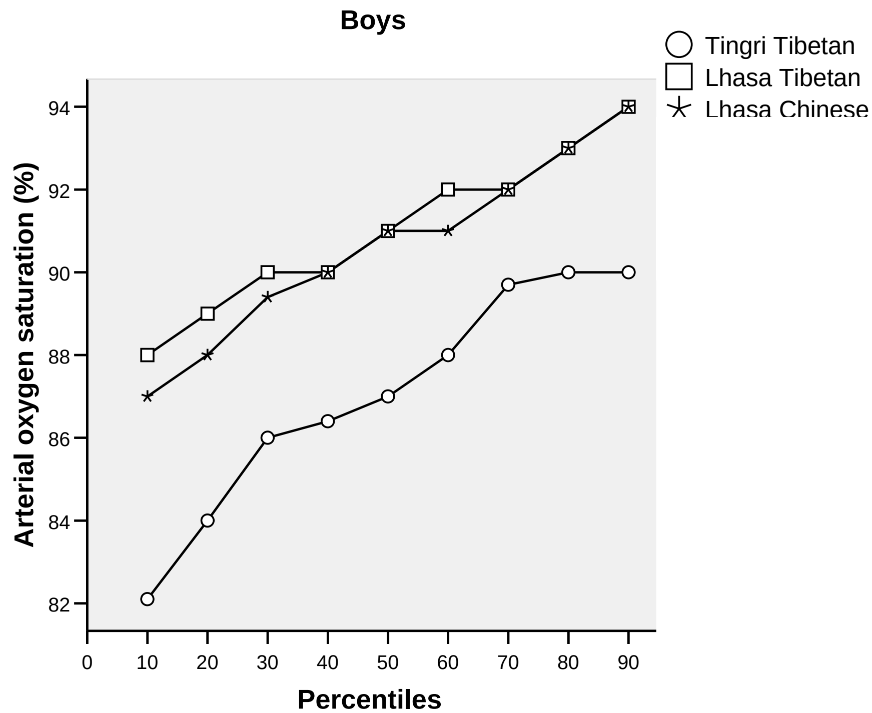


Figure 3. Arterial oxygen saturation at rest in 9-10 year old Tingri Tibetan, Lhasa Tibetan and Lhasa Han Chinese boys by percentiles

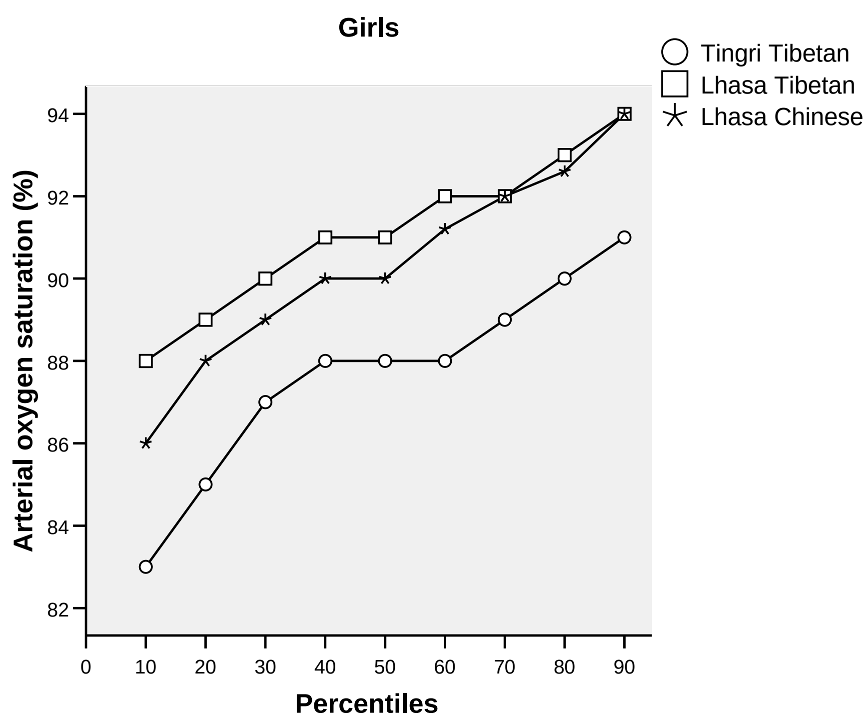


Figure 4. Arterial oxygen saturation at rest in 9-10 year old Tingri Tibetan, Lhasa Tibetan and Lhasa Han Chinese girls by percentiles

5 Lung function

Both Lhasa Tibetan boys and girls had higher ($p<0.001$) lung function values of FEV_1 and FVC as compared with Lhasa Chinese and Tingri Tibetan boys and girls, respectively (Table 6). Tingri Tibetan had lower FEV_1 and FVC values than the other two groups, except that there was no statistically significant difference between Tingri Tibetan girls and Lhasa Chinese girls for FVC. The lung function value of FEF_{50} was similar high in both Lhasa Tibetan boys and girls, and there was no statistically significant difference between Lhasa Chinese (boys and girls) and Tingri Tibetan (boys and girls).

FEV_1 and FVC were significantly positively associated with altitude, ethnicity, weight, and height in both boys and girls (not show in table). FEF_{50} was positively associated with weight in girls but not in boys, and was negatively associated with duration of living in Tibet in girls (not shown in table).

Table 7 shows lung function values after adjusting for age, weight, height, duration of living in Tibet, indicating that both Tingri Tibetan boys and girls have higher FEV_1, FVC and FEF_{50} values than Lhasa Tibetan children, who have higher values than Lhasa Chinese children. However, it was not statistically significant for the difference between Tingri and Lhasa Tibetan children for FEF_{50}.

Table 6. Lung function values in Tingri Tibetan, Lhasa Tibetan and Lhasa Chinese 9 to 10 year old schoolchildren.

	Boys			Girls		
	TingriTibetan N(195)	LhasaTibetan N(204)	LhasaChinese N(233)	TingriTibetan N(201)	LhasaTibetan N(193)	LhasaChinese N(164)
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
FEV_1 (L)	1.69** (1.66-1.72)	1.95 ᴼᴼ (1.92-1.99)	1.79△ △ (1.76-1.82)	1.60** (1.56-1.64)	1.85 ᴼᴼ (1.81-1.89)	1.70△ △ (1.67-1.74)
FVC (L)	1.94** (1.90-1.98)	2.22 ᴼᴼ (2.18-2.26)	2.04△ (2.00-2.08)	1.82** (1.78-1.86)	2.06ᴼᴼ (2.01-2.11)	1.89 (1.85-1.93)
FEF_{50} (L/s)	2.54** (2.46-2.62)	2.86 ᴼᴼ (2.76-2.96)	2.56 (2.48-2.64)	2.40** (2.31-2.49)	2.86 ᴼᴼ (2.76-2.95)	2.53 (2.43-2.63)

* $p < 0.05$ Tingri Tibetan VS Lhasa Tibetan, ** $p < 0.001$ Tingri Tibetan VS Lhasa Tibetan.

△ $p < 0.05$ Tingri Tibetan VS Lhasa Chinese, △ △ $p < 0.001$ Tingri Tibetan VS Lhasa Chinese.

ᴼ $p < 0.05$ Lhasa Tibetan VS Lhasa Chinese, ᴼᴼ $p < 0.001$ Lhasa Tibetan VS Lhasa Chinese.

Table 7. Adjusted lung function values in Tingri Tibetan, Lhasa Tibetan and Lhasa Chinese 9 to 10 year old schoolchildren.

	Boys			Girls		
	TingriTibetan N(195)	LhasaTibetan N(204)	LhasaChinese N(233)	TingriTibetan N(201)	LhasaTibetan N(193)	LhasaChinese N(164)
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
FEV1 (L)	1.91* (1.87-1. 94)	1.82 ^{OO} (1.79-1.85)	1.70$^{\triangle\triangle}$ (1.67-1. 74)	1.81** (1.77-1.84)	1.70 ^{OO} (1.67-1.73)	1.61$^{\triangle\triangle}$ (1.58-1.65)
FVC (L)	2.21** (2. 16-2.25)	2.05 ^{O} (2.01-2.08)	1.95$^{\triangle\triangle}$ (1.92-1.99)	2.05** (2.00-2.09)	1.89 ^{O} (1.86-1.93)	1.81$^{\triangle\triangle}$ (1.77-1.86)
FEF50 (L/s)	2.78 (2.65-2.91)	2.76 ^{OO} (2.66-2.86)	2.41$^{\triangle\triangle}$ (2. 29-2.52)	2. 75 (2. 62-2.87)	2.67 ^{OO} (2.57-2.77)	2.29$^{\triangle\triangle}$ (2.16-2.42)

Values were adjusted for age, weight, height, duration of living in Tibet.

* $p < 0.05$ Tingri Tibetan VS Lhasa Tibetan, ** $p < 0.001$ Tingri Tibetan VS Lhasa Tibetan.

$^{\triangle}$ $p < 0.05$ Tingri Tibetan VS Lhasa Chinese, $^{\triangle\triangle}$ $p < 0.001$ Tingri Tibetan VS Lhasa Chinese.

^{O} $p < 0.05$ Lhasa Tibetan VS Lhasa Chinese, ^{OO} $p < 0.001$ Lhasa Tibetan VS Lhasa Chinese.

6 Lung function and smoking habits

There was no statistically significant difference between adjusted lung function values and children who had or had not indoor smoking environments (Table 8).

Table 8. Mean values of FEV1, FVC and FEF50 in subgroups of individuals who reported indoor smoking/no smoking among Tingri Tibetan, Lhasa Tibetan and Lhasa Chinese 9 to 10 year old schoolchildren.

	Indoor smoking	FEV1(liter)	FVC(liter)	FEF50(liter)
		Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Tingri Tibetan	Yes	1.65 (1.63-1.68)	1.88 (1.85-1.91)	2.52 (2.43-2.60)
	No	1.63 (1.60-1.66)	1.87 (1.84-1.91)	2.42 (2.33-2.50)
Lhasa Tibetan	Yes	1.89 (1.87-1.92)	2.14 (2.11-2,16)	2.83 (2.75-2.91)
	No	1.90 (1.86-1.94)	2.12 (2.07-2.17)	2.94 (2.79-3.09)
Lhasa Chinese	Yes	1.75 (1.73-1.77)	1.97 (1.95-2.00)	2.53 (2.46-2.60)
	No	1.69 (1.65-1.74)	1.91 (1.86-1.97)	2.40 (2.24-2.56)

Values were adjusted for age, weight, height, duration of living in Tibet.

. Missing information varied between 2 and 15 for each of the item.

CHAPTER IV

DISCUSSION

IV Discussion

To our knowledge, the present study is the first epidemiological survey on 9-10 year old children living at different level of high altitude of sufficient sample size which include lung function, hemoglobin concentration and arterial oxygen saturation measurements. We found that native Tingri Tibetan children living in higher altitude (4300m) had significantly better adjusted FEV_1 and FVC than both Lhasa Tibetan and Lhasa Chinese children living in lower altitude (3700m). Lhasa Tibetan children had significantly higher adjusted FEV_1 and FVC values than Lhasa Chinese children, living at same altitude of 3700m. Both Tingri Tibetan and Lhasa Tibetan had higher adjusted FEF_{50} than Lhasa Chinese. Furthermore, the study showed that Tingri Tibetan children had significantly lower haemoglobin concentration than Lhasa Tibetan children and Lhasa Han Chinese children, while native Lhasa Tibetan children had lower haemoglobin concentration than Han Chinese children. The study also revealed that the Tingri Tibetan children had significantly lower arterial oxygen saturation than both Lhasa Tibetan and Lhasa Chinese children. In Lhasa, only Lhasa Tibetan girls had higher arterial oxygen saturation than Chinese girls.

1 Methodological discussion

The sample size calculation was based on the colleted data with lung function from Lhasa. The sample size gives sufficient power to detect a true difference as statistically significant between children living at different altitudes with respect to the main variables. Thus, we avoid failing to observe a difference when in truth there is one, which means Type Ⅱ error have been avoided.

We have done a limited number of statistical tests, so it is not likely that we have made Type Ⅰ error, observing a difference when in truth there is none.

Systematic error

In epidemiological observational studies there are always possibilities for systematic errors. The main problems to consider are: selection bias, information bias and confounding.

1.1 Selection bias

Selection bias is a systematic difference between people who are selected for a study and those who are not selected or a systematic difference between responders and non-responders (64). It usually occurs as a result of either using improper procedures for obtaining persons from the target population to become members of the study population or as a result of factors that influence participation of subjects in a study (65).

In the present study we randomly selected 5 primary schools from Tingri, and 9 primary schools from Lhasa. Thus, there should be no difference in characteristics between students who were invited to the study and those who were not. Even though it is six-year compulsory education in Tibet, there might be lower school attendance rate in the rural Tingri. It is, however, not likely that these differences may explain the observed differences. It could also be that sick and disabled children could not attend the school, but these situations have equal chance to happen in both Tingri and Lhasa children. This means that all 9-10 year old children living in higher altitude Tingri and Lower altitude Lhasa have the same chance to be invited to study, and thus, it is not likely that we have introduced bias in the selection of the sample.

The response rate was almost 100% both among Tingri and Lhasa children. Thus, no bias in the response has been introduced.

1.2 Information bias

Information bias is a flaw in measuring exposure or outcome data that results in different quality (accuracy) of information between comparison groups (66).

Before our study started, we did not know which group (Tingri Tibetan, Lhasa Tibetan and Lhasa Chinese) had the better lung function, and even during the data collection we just record the figures and did not observe the outcome. None of the groups were motivated to perform better than the others, which mean all the children were treated in the same way, and it is unlikely that the possible suspicion bias could be different between Tingri and Lhasa children. Tingri data was collected from September to October in 2007 and Lhasa data from August to November in 2005, both in the same season, but the temperature in Tingri was colder than in Lhasa. However, we did all the measurements indoor at each of the schools, and participates were tested under the same condition. Therefore, it is unlikely that it could have influenced the result significantly. All the field workers can speak and write the Tibetan and Chinese languages, and the local dialogue difference between Tingri and Lhasa Tibetan is very small. Therefore, both Tibetan and Chinese children can understand well what information we needed from them. However, it could be that these 9-10 year old children were too young to answer questions correct and had difficulties in remembering answers. However, recall bias exists in all cross- sectional studies, but possible errors should be equal in the three groups of children in Lhasa and Tingri.

The laboratory bias was possible in measurement of the hemoglobin concentration. However, we performed the measurement with a same experienced filed worker, therefore, it is not likely that this may influence the difference on hemoglobin concentration. All field workers in Tingri and in Lhasa were not from the same team, but we trained field workers exactly same measures both in Tingri and Lhasa very strictly, to be sure there were no difference criteria measurement between Tingri and Lhasa children.

1.3 Confounding

Confounding is a phenomenon when the association between an exposure and outcome is partial or totally explained by a third variable. This third variable is associated with both the exposure and outcome (67).

We restrict the participates in the study to the age of 9-10 year old students living in Tingri or Lhasa, thus, it is unlikely that age influence the results. Gender is a notorious confounder, as it is related to many aspects of life (68). Therefore, we present data for boys and girls separately to avoid interaction problems. Furthermore, we adjusted the lung function data for weight, height, and years living in Tibet.

2 Discussion of results

2.1 Hemoglobin concentration

Our findings that hemoglobin concentration was higher in Han than in Tibetan residents at same altitude (3700m) are consistent with previous reports (30;31;69-72). This may indicate that native Tibetans are better adapted to high altitude than Han Chinese. An increase in hemoglobin concentration with increasing altitude was reported as early as in the 1940s (73). It has been suggested (74) that 4% increase in the concentration of haemoglobin per 1000 m elevation can be used for the adjustment to different altitudes of the reference populations defined at sea level. However, for Tingri children, we found lower haemoglobin levels for both boys and girls as compared with Lhasa Tibetan and Lhasa Chinese children. This contradicts with previous studies (30;31;75). It could be Tingri Tibetan children maybe better adapted to high altitude than Lhasa children, because a study show that Sherpas do not have increased hemoglobin concentration levels and have higher affinity of blood for oxygen as compared with Caucasians living at 4000m (76), and show better adaptation to high altitude. It could also be because of Tingri Tibetan children had lower weight and height compared to Lhasa children, which may indicate malnutrition in Tingri Tibetan children. Among Tibetan children below the age of 36 months, rural children had prevalence of stunting of 41.4% and underweight of 24.7%, as compared with 25.3% and 18.1% respectively for urban children. And the rural children had a significantly lower Hb concentration (12.0 g/dl) than urban children (12.3 g/dl) (77). Further studies are needed to investigate a Hb-values and the possibility of iron deficiency and malnutrition among Tingri children, especially in rural areas. Suitable nutrition-education and iron supplementation programs may be recommended.

2.2 Arterial oxygen saturation

Our finding that the arterial oxygen saturation decreased with increasing altitude, which is in accordance with previous studies (36;78-80). We also found in Lhasa, that Tibetan girls had higher arterial oxygen saturation than Chinese girls. This may be because of variation in resting SaO_2 values appears to be heritable (81) and because Tibetans with higher SaO_2 values may be better adapted to hypoxic conditions than those with lower SaO_2 values (82). It has been reported that at an altitude of 2261 m the Han newcomers compared with Tibetan natives had similar SaO_2, both at rest and during exercise (39). At 4520 m, Tibetans had a slightly higher SaO_2 , and at 5620, even better SaO_2 than Han Chinese, both at rest and during exercise (39). Those with higher SaO_2 also have significantly better survival rates in high altitude (40;81). It was reported in healthy native Tibetans aged 1 week to 80 years living at 3800 to 4200 m, that Peak SaO_2 values were attained at 11 years of age after increasing from the first year of life, the peak value was essentially maintained through their forties and then declined markedly through their fifties and sixties (37). It was also reported among healthy Tibetan and Han newborn infants born in

Lhasa (3700m) (83), during a 4-month follow-up period, SaO_2 declined in the Han infants from 92% while awake and 90% while sleeping to 85% awake and 76% asleep at the age of 4 months. In the Tibetan infants, SaO_2 was 94% awake and 94% asleep just after birth and 88% awake and 86% asleep at the age of 4 months, suggesting that Tibetan infants sustained a higher SaO_2 than Han infants. However, in our study, we only investigated children from 9to10 years old. We found that, at same altitude, Lhasa Tibetan had higher arterial oxygen saturation and lung function than Lhasa Chinese. This may be indicating Tibetans have better adapted to the high altitude hypoxia and have less risk factors for later development of CMS than acclimatized newcomers or other lifelong high altitude residents (84).

2.3 lung function

Altitude may be important in determining the lung function. Native Tingri Tibetan children living at a higher altitude (4300m) had significantly higher FEV_1 and FVC than both Lhasa Tibetan and Lhasa Chinese children living at a lower altitude (3700m), which are in accordance with an epidemiologic survey among children and adults in New Guinea, it reported the highland population had larger values than the coastal population for lung function measurements of FEV_1 and FVC (85). An observation made among 10-12 year old Bolivian boys, also shows the high altitude children had higher FEV_1 in comparison to low altitude (86). In Ladakhi teenage boys and girls also showed higher FVC and FEV_1 in the high-altitude subjects than low altitude after adjusted for height and weight (87;88). A study among healthy African adults measured FVC and FEV_1 and found that altitude was the most important variable with an effect on FVC in men (89). Another study (90) compared lung function of FVC and FEV_1 between Han Chinese living at low altitude (250 m) near Beijing and Han chinese who were born and raised at three high altitudes (3,200 m, 3,800 m, 4,300 m) in Qinghai Province, P.R.C showed, after adjusting, mean FVC values among 6-21 year-old Han at high altitude were greater than those determined at a low altitude. These data indicate that growth at high altitudes produces small-to-moderate increases in lung function relative to genetically similar groups growing up at low altitudes. It is likely that the altitude at which people live affect the values of lung function. Changes in large airway size or in the elastic recoil of the lung affect FEV_1 and FVC (85) (91). FEF_{50} is a sensitive measure of small airway status (92). High landers who are exposed to hypoxia or low ambient pressure from birth may need to augment the airway or lung size to get enough oxygen to adapt to a high altitude. Therefore, altitude may play an important role in determining lung function. However, there are opposite results, which shows that the FVC values of a small number of Europeans living at 3050m above sea level in the united sates were similar to those of Europeans living at sea level (93).

We found in Lhasa, at the same altitude (3700m) that different ***ethnic*** groups had statistically different values of lung function. Native Lhasa Tibetan children had significantly higher FEV_1, FVC and FEF_{50} than the immigrated Han Chinese children. High lung function may be an important adaptation to the lifelong sustained increase in resting ventilation. A study (94) showed that Tibetans and Ladakhis have substantially higher values of lung function than predicted for Caucasians in the European Coal and Steel Community (ECSC) (47). To our knowledge, data on lung function of 9-10 years old Tibetans children with sufficient sample size are lacking. However, available literature on the spirometry of Asian subjects, including Indians, indicates similar or lower values than those for Caucasians (95;96). From these literature reviews and including the present one, we know that Tibetans have better lung function than other ethnic groups. In some respects, that could be why Han Chinese have higher prevalence of CMS than Tibetans.

In accordance with other studies (97-99) we found lung function values FEV_1 and FVC was significantly positively related with ***height*** and ***weight*** in all subjects. The FEF_{50} was significantly positively related with weight only in girls. Our finding is consistent with a study conducted among 7-15 year old Australian school children, the adjusted FVC and FEV_1 values increased significantly with increasing weight within each age and gender group and for all subjects combined (100). If the weight is exceeding normal value, it has a negative association with lung function (101). Obesity is associated with reduced lung function, Obesity is recognized to be associated with changes in pulmonary mechanics, particularly when it is extreme (101-103). We found in the present study that only 1.4% of Tibetan boys in Lhasa were obese which was the highest prevalence detected in subgroups of Tibetans, Han Chinese, boys, girls in Lhasa or Tingri.

The deleterious effects of ***passive smoking*** on the lung function of children have been reported in previous studies (104-106), Researchers from the Medical University in Vienna and Germany analysed data from a total of 22,712 children from eight countries. It was found that children of mothers who smoke were 30 percent to 40 percent more likely to have poor lung function than children born to non-smokers. Early-life exposure increased the risk of poor lung function to a lesser degree, by 24 percent to 27 percent (107). However, in our study, we found no effect on lung function in children with or without smoking environment. It could be due to recall bias, and also other indoor pollution. For example, most of the children, especially in Tingri, were exposed to traditional sources of energy (open fire wood and unprocessed biomass fuel such as yak and sheep dung) for cooking and heating. This clearly indicates that most of the children are heavily exposed to particles indoors, a type of exposure that has been suggested to cause harmful health effects. And exposure to indoor particles from wood and biomass fuel may level out differences in cigarette smoking. However it is still possible that exposure to indoor smoking environments could have caused poor lung function, but we were not able to discern such effect differences.

Other factors could also influence lung function. ***Physical activity*** is associated with a slower decline in pulmonary function and with lower mortality (108). In our study, Tingri children who live in a rural area are more likely to go to school on foot and have a long distance to walk compared with Lhasa children who live in the capital. Furthermore, the urban area is more competitive than rural area with respect to school work, Lhasa children have more extra lessons and homework than Tingri children, which means that Lhasa children have less leisure time to play than Tingri children. Tingri children may therefore be more physically active than Lhasa children, and thus, it may have contributed to better lung function than Lhasa children. However, we have not yet analyzed data on physical activity in the present study. With increasing evidence, ***low birth weight*** (LBW) has been reported to be associated with reductions in lung function in childhood, in both clinical (109-112)and population based studies (113;114). A large retrospective cohort study has demonstrated a significant link between LBW and a reduced adult lung function (115). However, the birth weight data of participants in the present study were not available. We found that the ***duration of living in Tibet*** had a statistically relationship with FEF_{50} in girls. The duration of living in high altitude may be an important factor influencing lung function. Therefore, children who live in high altitude for longer time had more chance to get natural training with lung while exposure to hypoxia or low ambient pressure. The Children's Health Study have monitored levels of ***air pollutants*** with lung function, and found that as children grow up, those who breathe smoggier air tend to lag in lung function growth behind children who breathe cleaner air (116). Children with decreased lung function may be more susceptible to respiratory disease and may be more likely to have chronic respiratory problems as adults. That could also be the reason why Lhasa children who live in more polluted air had lower function than Tingri children living in cleaner air. The fact that low ***socioeconomic status*** is associated with reduced lung function in male and female at all ages and in countries with markedly different standards of living and environmental exposures suggests multifactorial origins (117).

3 Conclusions and research recommendations

Native Tingri Tibetan children living at 4300m had higher adjusted lung function values of FEV_1 and FVC than Lhasa Tibetan children who had higher values than Lhasa Chinese children living at same altitude of 3700m. Both Tingri Tibetan and Lhasa Tibetan had higher FEF_{50} than Lhasa Chinese.

Furthermore, Tingri Tibetan children had significantly lower crude haemoglobin concentration than Lhasa Tibetan children and Lhasa Han Chinese children, while native Lhasa Tibetan children had lower crude haemoglobin concentration than Han Chinese children.

The study also revealed the Tingri Tibetan children had significantly lower crude arterial oxygen saturation than both Lhasa Tibetan and Lhasa Chinese children. In Lhasa, only Lhasa Tibetan girls had higher arterial oxygen saturation than Chinese girls.

If poor lung function in children is associated with increased risk of CMS at older age, the results indicate that Tingri Tibetan children have lower risk of CMS than Lhasa Tibetan children, although the prevalence of CMS should be higher at 4300 m than 3700 m. It follows that lung function will change differently for native Tibetan in Tingri and Lhasa with increasing age and/or that other factors are of more importance for the risk of CMS development. It also seems that Lhasa Han Chinese will have a higher risk of CMS than Lhasa Tibetans.

A prospective study, following the children to the age when CMS occur would give an answer to this hypothesis. Regarding hemoglobin concentration and arterial oxygen saturation, the crude analysis may indicate that the Tingri Tibetan children are better adapted to living at a high altitude as compared with Lhasa Tibetan and Lhasa Chinese children. However, further adjusted analyses must be done in order to compare the different groups.

Normal lung function values and ranges are conventionally calculated according to variables such as age, sex, height, and weight, which contribute independently to predictions of lung function (118). Studies on lung function prediction equations for FVC and FEV_1 have been carried out on European, Afro-Caribbean and Indian children (119-121). They have clearly established that there was a large variance among lung functions in these populations. As far as we know, there are no lung function prediction equations for Tibetan children aged 9-10 living at 3700 meters and 4300 meters above sea level high. Therefore, it is meaningful to establish a lung function standard for Tibetan children, which may be established based on our lung function data.

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Appendix I

Background on Tibet Autonomous Regions

Geography

The Tibet Autonomous Region (TRA) is located on the Qinghai-Tibetan Plateau, with an average elevation of over 4,000 meters, it is the highest region on earth and is commonly referred to as the "Roof of the World ". It borders on Sichuan and Yunnan province to the east, Qinghai and Xingjiang to the north in china, and shares borders with India, Nepal, Sikkim, Bhutan, and Burma to the south, and borders by Kashmir to the west. It has an area of 1.2 million square kilometers and less than 2.1 people per square kilometer (122).

Demography

According to the Population Census in 2000, there are 2,616,300 people in Tibet, with Tibetans totaling 2,411,100 (92.2%), Han 155,300 (5.9%) and 49,900 (1.9%) from other ethnic groups which include: Menpa, Luopa, Hui, Sherpa and a few Deng people living in Tibet (123). From the official figure in 2003, the average life expectancy was 67 years for both sexes (57). The total fertility rate was 4.36 children/women in 1989, and it declined to 3.0 in 2000 (124;125). The illiterate rate decreased from 44.4% in 1990 to 32.5% in 2000. In 2000, the enrollment rate of school-age children was 85.8%, which was the lowest in China. The educational level of females was lower than males (126).

Economy

The Tibetan economy has developed in recent years. In 2004, Tibet's gross domestic product (GDP) topped 21.15 billion Yuan (US$2.57 billion), almost double the year 2000 figure of 11.75 billion Yuan (US$1.43 billion) (127). The per capita disposable incomes of the urban and rural residents in Tibet averaged 8,200 yuan (US$1,025) and 1,861 yuan (US$232) respectively in 2004 (127). While traditional agricultural and animal husbandry industries continue to play a leading role in the local economic development. The main livestock in Tibet are sheep, cattle, goats, camels, yaks and horses. The main crops grown are barley, wheat, buckwheat, rye, potatoes and assorted fruits and vegetables. In addition to vast salt reserves, Tibet has large deposits of gold, copper, and radioactive ores. However, Tibet remains an underdeveloped region, where there are still 210,000 people living in poverty (128).

Diet

The most important crop in Tibet is barley, and dough made from barley flour called (Tsampa), is the staple food of Tibet. This is either rolled into noodles or made into steamed dumplings called momos. Meat dishes are likely to be yak, goat, or mutton, often dried, or cooked into a spicy stew with potatoes. Mustard seed is cultivated in Tibet, and therefore features heavily in its cuisine. Yak yoghurt, butter and cheese are frequently eaten, and well-prepared yoghurt is considered something of a prestige item. Butter tea is very popular to drink, most Tibetans drink butter tea in the morning, with Tsampa for the breakfast, some of them drink butter tea whole day.

School system

By now there are over 4,000 schools of various kinds at different levels in Tibet, of which 820 are primary schools, 3033 teaching centers, over 110 middle and vocational schools, 4 colleges. Meanwhile, the quality of more than 19,000 teachers, consisting mainly of Tibetans, has also been improved steadily. Up to now, the percentage of educationally qualified teachers has respectively reached 67%, 77%, and 65% in primary schools, junior and senior middle schools (129).

The average age for children go to school is 7 years old in Tibet. The children from the rural areas usually start later than children in the city or urban areas. The primary education in Tibet is the six-year compulsory education. The students who complete primary school education have a chance to enter a six-year high school. The high school is divided into junior high school and senior high school, each for three years duration. After graduated from high school they can take exam to apply for colleges. Some of them go to vocational schools after they finished the junior high school (130).

Appendix II

Application for conducting field work

To whom it may concern,

I am a teacher from Tibet University Medical College. I am studying for the master degree of International Community Health in University of Oslo in Norway. I have returned for conducting my field work in Tingri. The title of my project is "The lung function, hemoglobin concentration and arterial oxygen saturation among 9-10 year old native Tibetan and Han Chinese children living at 3700meters and 4300meters above sea level in Tibet". The aim of the present study is to investigate differences between Lhasa children (living at 3700 meters above sea level) and Tingri Tibetan children (living at 4400 meters above sea level) with respect to selected factors, which may be potential risk factors for later development of CMS, such as lung function, hemoglobin concentration, arterial oxygen saturation. The results from this study will be utilized for the purpose of increase the awareness of CMS and its public health consequences, and to provide data which may contribute to the understanding of CMS.

Questionnaire, lung function measurement, haemoglobin concentration measurement and oxygen saturation measurement will be applied in this study. Around 400 school children who were born between 1st of January and 31st of December in 1997 will be chosen. The subjects will be recruited from volunteers who can refuse to participate and withdraw from the study for any reason at any time without any consequences for themselves. Parents will on behalf of their children participate in this study. All information about the subjects will be handled confidentially.

This study will chose schools randomly from all the primary schools in Tingri. Therefore, we sincerely expect to get permission form Education Office of TAR, each school and parents.

Gonggalanzi

Tibet University Medical College

Appendix III

Consent Form

Dear participants,

I am a teacher from Tibet University Medical College. I am studying for the master degree of International Community Health at the University of Oslo in Norway. I have returned to conduct my field work in Tingri. The title of my project is "The lung function, hemoglobin concentration and arterial oxygen saturation among 9-10 year old native Tibetan and Han Chinese children living at 3700meters and 4300meters above sea level in Tibet". We have already collected data on lung function, hemoglobin concentration, and arterial oxygen saturation from Lhasa in 2005. The aim of the present study is to investigate differences between Lhasa children (living at 3700 meters above sea level) and Tingri Tibetan children (living at 4400 meters above sea level) with respect to selected factors, which may be potential risk factors for later development of CMS, such as lung function, hemoglobin concentration, arterial oxygen saturation.

Around 400 school children who were born between 1st of January and 31st of December in 1997 will be chosen. All of participants are to voluntarily participate in this study. Participants have the right to abstain from participation in the study or to withdraw consent to participate at any time for any reason without any consequence. All information about the subjects will be handled confidentially. Questionnaire, lung function measurement, haemoglobin concentration measurement and oxygen saturation measurement will be used in this study. Participant need to fill questionnaire under supervision of a researcher. These tests which we will perform in my study are very safe, there is almost no risk in tests, and participants will not participate in any procedures which may have potential harm to them. Because children just need to expire as fast, hard and long as possible with mouth piece to test lung function. The arterial oxygen saturation sensor will be attached around the index finger to test arterial oxygen saturation. To determine hemoglobin concentration we need to collect a drop of blood from a finger tick for hemoglobin concentration. Utmost care will be provided to avoid injury and infection to the participants, disinfection will be done with strictness. If the participant suffers any risk that is directly from participating in the study, the investigator will arrange for treatment and care in the Government health care system with personal obligation.

The results from this study will be utilized for the purpose of increasing the awareness of CMS and its public health consequences, and to provide data which may contribute to the understanding of CMS. The result of the study will be sent to each of participant by mail following data analysis to thank for contributions to the study.

We expect to get permission from all the parents or superiors of the participants.

We sincerely thank you for your cooperation!

Medical College of the University of Tibet

Do you agree to participate in the study?

I agree……………………… No I don't agree…………………..

Signature___________________ Date:_____________________

Appendix IV

Questionnaire (Childhood Health in Lhasa, Tibet)

No.□ □ □ □ □ □ □

Date of answering the questionnaires: / /2007

Part Ⅰ

Core questionnaire for demographic characteristics

1.Name of school:
2.Name of Village and Town:
3.Name of County:
4.Name of District:
5.Name of you:
6.____ Class ____ Grade

7. Are you a boy or girl? Boy□ 1 Girl□ 2

8. How old are you?_______ Years old

9. How many brothers do you have （including dead brothers）?
Older brothers
Younger brothers

10.How many of your older brothers are dead?
Which of the following reasons caused his or their death?
1.Drowning 2. Pneumonia 3.Tuberculosis 4.Traffic Accident 5.Trauma
6. Get an electric shock 7. Pesticide poisoning 8. Cardiopathy 9. Gastroenteritis
10.Others

11.How many of your younger brothers are dead?
Which of the following reasons caused his or their death?
1.Drowning 2. Pneumonia 3.Tuberculosis 4.Traffic Accident 5.Trauma
6. Get an electric shock 7. Pesticide poisoning 8. Cardiopathy 9. Gastroenteritis
10.Others

12. How many sisters do you have（including dead brothers?
Older sisters
Younger sisters

13. How many of your older sisters are dead?
Which of the following reasons caused her or their death?
1.Drowning 2. Pneumonia 3.Tuberculosis 4.Traffic Accident 5.Trauma
6. Get an electric shock 7. Pesticide poisoning 8. Cardiopathy 9. Gastroenteritis
10.Others

14. How many of your younger sisters are dead?
Which of the following reasons caused her or their death?
1.Drowning 2. Pneumonia 3.Tuberculosis 4.Traffic Accident 5.Trauma
6. Get an electric shock 7. Pesticide poisoning 8. Cardiopathy 9. Gastroenteritis
10.Others

15. Where were you born?
Lhasa□ 1 Shigatse□ 2 Nyingchi□ 3 Lhoka □ 4 Chamdo□ 5
Nagchu□ 6 Ngari□ 7 Others___________ 8

16. What ethnic group do you belong to?
Tibetan□ 1 Han Chinese □ 2 Han Moslem □ 3 Tibetan Moslem □ 4
Others___________ 5

17. What language do you speak mainly in your family?
Tibetan□ 1 Chinese□ 2 Tibetan and Chinese□ 3 Others_____4

18. Do you know anything about ASTHMA?
Yes□ 1 No□ 2
If yes, how did you know it?
(Please tick all that apply)

	Yes□ 1	No□ 2
From your parents	□	□
From your sisters or brothers	□	□
From your friends	□	□
From your teachers	□	□
From books / newspapers	□	□
From radio / TV	□	□
Others____________	□	□

Part II
Video questionnaire

19. Has your breathing <u>ever</u> been like this at any time in your life?

Yes□ 1 No□ 2

If yes, has this happened in the past 12 months? Yes□ 1 No□ 2

If yes, has this happened at least once a month? Yes□ 1 No□ 2

20. Has your breathing been like the boy's in the dark shirt following exercise at any time in your life? Yes□ 1 No□ 2

If yes, has this happened in the past 12 months? Yes□ 1 No□ 2

If yes, has this happened at least once a month? Yes□ 1 No□ 2

21. Have you been woken at night like this at any time in your life?

Yes□ 1 No□ 2

If yes, has this happened in the past 12 months? Yes□ 1 No□ 2

If yes, has this happened at least once a month? Yes□ 1 No□ 2

22. Have you been woken at night like this at any time in your life?

Yes□ 1 No□ 2

If yes, has this happened in the past 12 months? Yes□ 1 No□ 2

If yes, has this happened at least once a month? Yes□ 1 No□ 2

23. Has your breathing <u>ever</u> been like this at any time in your life?

Yes□ 1 No□ 2

If yes, has this happened in the past 12 months? Yes□ 1 No□ 2

If yes, has this happened at least once a month? Yes□ 1 No□ 2

Part Ⅲ

Core questionnaire for wheezing and asthma

24. Have you <u>ever</u> had wheezing or whistling in the chest at any time in the past?

Yes□ 1 No□ 2

If you have answered 'NO', please jump to question 30.

25. Have you had wheezing or whistling in the chest <u>in the past 12 months</u>?

Yes□ 1 No□ 2

If you have answered 'NO', please jump to question 30.

26. How many attacks of wheezing have you had <u>in the past 12 months</u>?

None☐ 1 1 to 3☐ 2 4 to 12☐ 3 More than 12☐ 4

27. <u>In the past 12 months</u>, how often, on average, has your sleep been disturbed due to wheezing?

Never woken with wheezing☐ 1 Less than one night per week☐ 2

One or more nights per week☐ 3

28. <u>In the past 12 months</u>, has wheezing ever been severe enough to limit your speech to only one or two words at a time between breathes?

Yes☐ 1 No☐ 2

29. <u>In the past 12 months</u>, what have made your wheezing worse? (Please tick all that apply)

	Yes☐ 1	No☐ 2
Weather	☐	☐
Pollen	☐	☐
Emotion	☐	☐
Fumes	☐	☐
Dust	☐	☐
Pets	☐	☐
Wool clothing	☐	☐
Colds or ‘flu	☐	☐
Cigarette smoke	☐	☐
Food or drinks	☐	☐
Soaps, sprays or	☐	☐
Detergents	☐	☐
Drug (Aspirin)	☐	☐

Others (please list below)

30. Have you <u>ever</u> had asthma?

Yes☐ 1 No☐ 2

31. <u>In the past 12 months</u>, has your chest sounded wheezy during or after exercise?

Yes☐ 1 No☐ 2

32. In the past 12 months, have you had a dry cough at night, apart from a cough associated with a cold or chest infection?

Yes□ 1 No□ 2

33. Questions about what activities usually make you feel breathless.

Sitting or lying still □ 1 Getting washed or dressed □ 2

Walking around the home □ 3 Walking outside on the level □ 4

Walking up a flight of stairs □ 5 Walking up hills□ 6

Playing sports or games □ 7

Part Ⅳ

Core questionnaire for rhinitis

All questions are about problems which occur when you DO NOT have a cold or the 'flu.

34. Do you have snivel custom in your life?

	Yes□ 1	No□ 2
In the past	□	□
At present	□	□

35. Have you ever had a problem with sneezing or a runny or blocked nose, when you DID NOT have a cold or the 'flu?

Yes□ 1 No□ 2

If you have answered 'NO', please jump to question 40.

36. In the past 12 months, have you had a problem with sneezing or a runny or blocked nose when you DID NOT have a cold or the 'flu?

Yes□ 1 No□ 2

If you have answered 'NO', please jump to question 40.

37. In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?

Yes□ 1 No□ 2

38. In which of the past 12 months did this nose problem occur? (Please tick all that apply)

January□ 1 February□ 2 March□ 3 April□ 4 May□ 5 June□ 6 July□ 7

August□ 8 October□ 9 September□ 10 November□ 11 December□ 12

39. In the past 12 months, how much did this nose problem interfere with your daily activities?

Not at all□ 1 A little□ 2 A moderate amount□ 3 A lot□ 4

40. Have you ever had hay fever?

Yes□ 1 No□ 2

Part V

Core questionnaire for eczema

41. Have you ever had an itchy rash that was coming and going for at least six months?

Yes□ 1 No□ 2

If you have answered 'NO', please jump to question 46.

42. Have you had this itchy rash at any time in the past 12 months?

Yes□ 1 No□ 2

If you have answered 'NO', please jump to question 46.

43. Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, of around the neck, ears or eyes?

Yes□ 1 No□ 2

44. Has this rash cleared completely at any time during the past 12 months?

Yes□ 1 No□ 2

45. In the past 12 months, how often, on average, have you been kept awake at night by this itchy rash?

Never in the last 12 months□ 1 Less than one night per week□ 2

One or more nights per week□ 3

46. Have you ever had eczema?

Yes□ 1 No□ 2

47.Have you ever had rhinitis?

Yes□ 1 No□ 2

Part Ⅵ

Cough and phlegm

48.<u>In the past 12 months</u>, have you usually seemed congested in the chest or coughed up phlegm (mucus) with colds?

Yes□ 1 No□ 2

49.<u>In the past 12 months</u>, have you usually seemed congested in the chest or coughed up phlegm (mucus) when you did <u>not</u> have a cold?

Yes□ 1 No□ 2

If you have answered 'NO' to <u>both</u> of these questions, please jump to questions 52.

50.Do you seem congested in the chest or cough up phlegm (mucus) on most days (4 or more days a week) for as much as 3 months of the year?

Yes□ 1 No□ 2

If you have answered 'NO', please jump over question 51.

51.For how many years have this happened?______ Years

52.Do you have experienced number of episodes last year?

Ear infection__ Throat infection__ Headache__ Fever

If yes, how many times of the following health problems have you had during the last year?

Ear infection__ Throat infection__ Headache__ Fever

Part Ⅶ

Core questionnaire for your living (environment)

53. Do or did you share the bedroom with other people?

	Yes□ 1	No□ 2
In the past	□	□
At present	□	□

With how many people did you share the bedroom in the past?
With how many people do you share the bedroom at present?

54. Which of the following pets do or did you keep inside your home? (Please tick all that apply)

	Dog□ 1	Cat□ 2	Bird□ 3	Rabbit□ 4	Other animal□ 5	No pets□ 6
In the past	□	□	□	□	□	□
At present	□	□	□	□	□	□

55. Do or did you have at least once a week contact with any of the following animals outside your home? (Please tick all that apply)

	Dog☐ 1	Cat☐ 2	Farm animals (cow, sheep, goat, horse) ☐ 3	Other animals☐ 4
In the past	☐	☐	☐	☐
At present	☐	☐	☐	☐

56. Does your mother smoke?

	Yes☐ 1	No☐ 2
Formerly	☐	☐
Currently	☐	☐

57. Does your father smoke?

	Yes☐ 1	No☐ 2
Formerly	☐	☐
Currently	☐	☐

58. Has anyone smoked in the past or present inside your home?

Yes☐ 1 No☐ 2

If yes, how many cigarettes in total are smoked by all smokers per day in your home? (Mother smokes and father smokes and other persons smoke)

Less than 10 cigarettes☐ 1 10 to 20 cigarettes☐ 2 More than 20 cigarettes☐ 3

In the past
At present

59. Which fuels do or did you use for cooking? (Please tick all that apply)

Yes☐ 1 No☐ 2

	Electricity	Gas	Coal	Kerosene/ Patrol
In the past	Yes☐ No☐	Yes☐ No☐	Yes☐ No☐	Yes☐ No☐
At present	Yes☐ No☐	Yes☐ No☐	Yes☐ No☐	Yes☐ No☐

	Wood	Yak/Sheep dung	Others
In the past	Yes☐ No☐	Yes☐ No☐	Yes☐ No☐
At present	Yes☐ No☐	Yes☐ No☐	Yes☐ No☐

60. Which fuels do or did you use for heating? (Please tick all that apply)

Yes☐ 1 No☐ 2

Electricity Gas Coal Kerosene/ Patrol

In the past	Yes□ No□	Yes□ No□	Yes□ No□	Yes□ No□
At present	Yes□ No□	Yes□ No□	Yes□ No□	Yes□ No□

	Wood	Yak/Sheep dung	Others
In the past	Yes□ No□	Yes□ No□	Yes□ No□
At present	Yes□ No□	Yes□ No□	Yes□ No□

61. Does your family or parents own any of the following appliances?

	Yes□ 1	No□ 2
Television	□	□
Radio	□	□
Car	□	□
Tractor	□	□
Motorcycle	□	□
Bicycle	□	□
Computer	□	□
Telephone	□	□
Mobil phone	□	□

62. How far is your home from the main road?

Less than 10m□ 1 11 to 30 m□ 2 31 to 50 m□ 3 50 to 100m□ 4

More than 100m□ 5

63.What kind of road is it?

Dust road□ 1 Concrete or cement road□ 2 Blacktop road□ 3

64.What kind of vehicle do you take from your house to school usually?

Truck□ 1 Tractor□ 2 Car□ 3 Motorcycle□ 4 Bicycle□ 5 Walk□ 6 Others□ 7

65. Does or did your home have damp spots on the walls or ceiling?

	Yes□ 1	No□ 2
In the past	□	□
At present	□	□

66. Does or did your home have visible moulds or fungus on the walls or ceiling?

Yes□ 1 No□ 2

In the past ☐ ☐

At present ☐ ☐

67. What kind of floor covering is or was there in your bedroom? (Please tick all that apply)

Yes☐ 1 No☐ 2

	Wool carpet	Synthetic fiber carpet	Plastic carpet
In the past	Yes☐ No☐	Yes☐ No☐	Yes☐ No☐
At present	Yes☐ No☐	Yes☐ No☐	Yes☐ No☐

	No carpet	Others
In the past	Yes☐ No☐	Yes☐ No☐
At present	Yes☐ No☐	Yes☐ No☐

68. How many windows do or did you have in your bedroom?

Yes☐ 1 No☐ 2

	One	Two	More than two	No window
In the past	Yes☐ No☐	Yes☐ No☐	Yes☐ No☐	Yes☐ No☐
At present	Yes☐ No☐	Yes☐ No☐	Yes☐ No☐	Yes☐ No☐

If you have answered "No window", please jump to question 70.

69. What kind of windows is or was there in your bedroom?

Yes☐ 1 No☐ 2

	Single glazing	Double glazing	Wood	Paper
In the past	Yes☐ No☐	Yes☐ No☐	Yes☐ No☐	Yes☐ No☐
At present	Yes☐ No☐	Yes☐ No☐	Yes☐ No☐	Yes☐ No☐

	Nothing
In the past	Yes☐ No☐
At present	Yes☐ No☐

70. What kind of pillows do or did you use? (Please tick all that apply)

Yes☐ 1 No☐ 2

	Foam	Wool	Feather	Dry grass
In the past	Yes☐ No☐	Yes☐ No☐	Yes☐ No☐	Yes☐ No☐
At present	Yes☐ No☐	Yes☐ No☐	Yes☐ No☐	Yes☐ No☐

	No use	Others
In the past	Yes☐ No☐	Yes☐ No☐
At present	Yes☐ No☐	Yes☐ No☐

71. What kind of beddings do or did you use? (Please tick all that apply)

Yes□ 1 No□ 2

	Wool	Synthetic fibre	Feather	Blankets
In the past	Yes□ No□	Yes□ No□	Yes□ No□	Yes□ No□
At present	Yes□ No□	Yes□ No□	Yes□ No□	Yes□ No□

	Cotton	Other material
In the past	Yes□ No□	Yes□ No□
At present	Yes□ No□	Yes□ No□

72. Outside school hours, how often do you usually exercise so much that you get out of breath or sweat?

Every day□ 1 4 to 6 times a week□ 2 2 to 3 times a week□ 3

Once a week□ 4 Once a month□ 5 Less than once a month□ 6

73. How often, on average, do you eat or drink the following, nowadays? (Please tick all that apply)

Never□ 1 Less than once per week□ 2 1 to 2 times per week□ 3 3 to 6 times per week□ 4 Once per day or more often□ 5

Meat □ Fish □ Fruits □ Vegetables □ Legumes (peas, beans) □

Flour □ Rice □ Butter □ Fizzy drinks □ Potatoes □ Milk □

Egg □ Cooked vegetables □ Burger □ Juice □ Nuts □

Hot Pot □ Instant noodles □ Dry beef □ Dry lamb □ Cheese □

Tsamba □ Chang □

74. Please indicate how good your health is now:

Very good□ 1 Good□ 2 Quite good□ 3 Bad□ 4

75.Do you have any health problems?

Yes□ 1 No□ 2

If yes, please list here:

76. Are you usually feeling hungry when you go to bed at night?

Yes□ 1 No□ 2

If yes, how many times a week?

Once□ 1   Twice□ 2   Three times□ 3 Four to five times□ 4 Every night□ 5

Part VIII

Core questionnaire for habitual physical activity ***(Please tick only one)***

77. How do you usually travel to school?
by car or motorcycle□ 1   by bus□ 2   by bicycle □ 3   by foot□ 4

78. How do you usually travel home from school?
by car or motorcycle□ 1   by bus□ 2   by bicycle□ 3   by foot□ 2

79. How long does it usually take you to travel to school from your home?
less than 5 minutes□ 1   5 to 15 minutes□ 2   15 to 30 minutes□ 3
30 minutes to 1 hour□ 4   more than 1 hour□ 5

80. How many days a week do you go from home to school? __________ days

81. What do you normally do at morning break?
sit down (talking, reading)□ 1   stand, walk around□ 2
run around playing games□ 3

82. What do you normally do at lunch break (apart from eating lunch)?
sit down (talking, reading) □ 1   stand, walk around□ 2
run around playing games□ 3   go home for lunch □ 4

83. Which of these is most like you?
I don't exercise□ 1   I exercise sometimes but not regularly□ 2
I exercise regularly□ 3

84. Which of these is most like you?
Either
I don't exercise and I don't intend to start□ 1
I don't exercise but I might start□ 2
Or
I exercise regularly but have just started to do so□ 3
I exercise regularly and have for over 6 months□ 4

85. It's up to me when I play games or sport

Definitely yes☐ 1 Maybe☐ 2 Definitely no☐ 3

86. I have more fun playing games and sports than doing other things
    Definitely yes☐ 1 Maybe☐ 2 Definitely no☐ 3

87. Playing games and sports is the thing I like to do best
    Definitely yes☐ 1 Maybe☐ 2 Definitely no☐ 3

88. I wish I could play more games and sports than I get a chance to
    Definitely yes☐ 1 Maybe☐ 2 Definitely no☐ 3

89. At school there are playgrounds or fields where I can run around
    Definitely yes☐ 1 Maybe☐ 2 Definitely no☐ 3

90. How often do you stay behind at school to take part in exercise
    Hardly ever or never☐ 1 Once or twice a week☐ 2
    Most days☐ 3 Every day☐ 4

91. How often do you play games outside after school
    Hardly ever or never☐ 1 Once or twice a week☐ 2
    Most days☐ 3 Every day☐ 4

If I went to do exercise most days....

92. It would get or keep me in shape
    Definitely yes☐ 1 Maybe☐ 2 Definitely no☐ 3

93. It would make me better in sports
    Definitely yes☐ 1 Maybe☐ 2 Definitely no☐ 3

94. It would be fun
    Definitely yes☐ 1 Maybe☐ 2 Definitely no☐ 3

95. It would help me be healthy
    Definitely yes☐ 1 Maybe☐ 2 Definitely no☐ 3

96. It would help me control my weight
    Definitely yes☐ 1 Maybe☐ 2 Definitely no☐ 3

If I were to exercise most days...

97. It would give me energy

Definitely yes☐ 1 Maybe☐ 2 Definitely no☐ 3

98 It would help me make new friends

Definitely yes☐ 1 Maybe☐ 2 Definitely no☐ 3

99. It would help me be with my friends more

Definitely yes☐ 1 Maybe☐ 2 Definitely no☐ 3

100. It would help me look good to others

Definitely yes☐ 1 Maybe☐ 2 Definitely no☐ 3

101. Do you want to take part in our follow-up study?

Yes☐ 1 No☐ 2

Part Ⅸ

Ⅸ-Ⅰ Physical examination

102. Weight (Kg):_______ □ □ .□

103. Height (cm):_______ □ □ □ .□

104. Seat Height (cm):_____ □ □ .□

Circumference (cm)

105.Head:______ ①□ □ .□ ②□ □ .□

106.Chest: ____ ①□ □ .□ ②□ □ .□

107.Belly: ____ ①□ □ .□ ②□ □ .□

108. Immunization (vaccination)?

Nothing □ 1 Scar□ 2 Node□ 3

Ⅸ-Ⅱ Lung function test (It will be registered automatically on computer)

FEV_1 □ □ .□

FVC □ □ .□

FEF_{50} □ □ .□

Ⅸ-Ⅲ Hemoglobin and Glucose test

Hemoglobin: ☐ ☐ .☐ Glucose: ☐ ☐ .☐

Ⅸ-Ⅳ Bicycle test

Time (min)	Workload (watt)	HR (beats/min)	SpO_2 (%)	
Rest	Lying down for 2-3min			
0	20 / 25			
3	40 / 50			
6	60 / 75			
9	80 / 100			
12	100 / 125			
15	120 / 150			Finished time (min)
18	140 / 175			

You have now finished. Thank you very much!!!